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PRINCIPAL INVESTIGATOR: David J. Getty, Ph.D.

CONTRACTING ORGANIZATION: BBN Technologies Solutions LLC
Cambridge, MA 02138

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14. ABSTRACT The goal of this project was to evaluate, in a screening context, stereoscopic digital mammography versus standard (non-stereo) digital mammography for earlier detection of breast lesions during screening and for reduction in the rate of patient recall for further work-up. We enrolled 1458 patients at elevated risk for the development of breast cancer into the clinical trial. Each patient received both a standard screening examination and a stereoscopic screening examination which were read independently by different radiologists. If a suspicious finding was reported from either reading, the patient was recalled for standard clinical workup examinations, which formed the basis for lesion truth. Compared to standard digital mammography, stereo mammography significantly reduced false positive lesion detections by 46% ($p < 0.0001$), and significantly increased true positive lesion detections by 23% ($p < 0.05$). ROC analysis of the readers' judgments of the likelihood that a reported finding is real showed significantly greater accuracy for stereo, $A_z = 0.94$, than for standard, $A_z = 0.85$ ($p = 0.004$).					
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INTRODUCTION

The objective of this project was to evaluate stereoscopic digital mammography compared to standard (non-stereo) digital mammography for detection of true breast lesions (benign or malignant) in a screening population of patients at elevated risk for development of breast cancer. We hypothesized that stereo mammography, by enabling the mammographer to view the internal structure of the breast in depth, would support earlier and more accurate detection of subtle breast lesions and also support more confident dismissal of normal or clearly benign cases. We expected, as a consequence, that stereo mammography would perform better than standard mammography with both greater sensitivity and greater specificity in the detection of abnormalities in the breast, and with a reduced rate of unnecessary recall.

At the end of the clinical trial in December, 2007, 1458 women, each at elevated risk for development of breast cancer because of personal or family history, were enrolled in the project and received both standard (non-stereo) and stereoscopic digital mammography screening examinations. The standard and stereo mammographic images were interpreted in independent readings by different mammographers. The reading data were analyzed to determine the comparative rates of true lesion detection, and of appropriate recall for further work-up.

Compared to standard digital mammography, stereo mammography significantly reduced false positive lesion reports by 46% ($p < 0.0001$), and significantly increased true positive lesion detections by 23% ($p < 0.05$). ROC analysis of the readers' ratings of the likelihood that a reported finding is a true lesion showed significantly greater accuracy for stereo, $Az = 0.94$, than for standard, $Az = 0.85$ ($p = 0.004$).

The results of this project show that stereo mammography is more accurate than standard mammography in detecting true lesions in breast cancer screening, both in reducing false positive reports by nearly half while also improving the detection of true lesions.

We have organized the body of this Final Report according to the six Tasks that were laid out in the project's Statement of Work.

BODY OF REPORT

1. Task 1: Development of the stereoscopic digital mammography display workstation

1.1. Development of the original CRT-based Stereoscopic Display Workstation

During the first year of the project we built two copies of the CRT-based stereo display workstation, one of which is shown in Figure 1. In this system, the two images forming a stereo pair were displayed alternately on the same CRT face, at a high frame rate (120 Hz). The user wore active LCD glasses that served as electronic shutters, alternately opening the shutter of one eye while closing the other, and then reversing. The glasses were synchronized to the display controller card such that when the Left eye image was displayed, the Left eye shutter was open, and when the Right eye image was displayed, the Right eye shutter was open. The one advantage of this method of stereo display is that there are no image alignment issues since both images are displayed sequentially on the same monitor.

One workstation was located at BBN and the other was installed at the Emory Breast Clinic at Emory University, for use by the mammographers participating in the project. Just before we were ready to start enrolling patients into the study, the display controller card in the workstation at Emory failed. This card, a Dome MD8 card modified by Planar to support stereoscopic display, was a member of the MD series of analog display controller cards. These were no longer being manufactured by Planar, and had been replaced by a series of digital display controller cards. Planar attempted to repair the MD8 card, but found that several of the electronic components needed for the repair were no longer available.

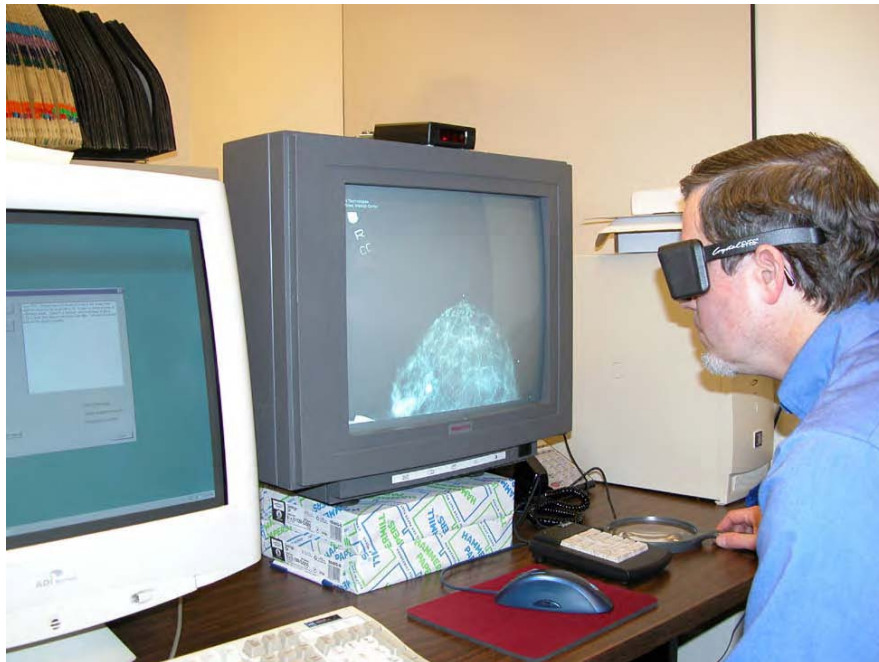


Figure 1. CRT-based stereoscopic display workstation.

1.2. Development of a new LCD-based stereoscopic display workstation

Fortunately, Planar was already pursuing the development of a new stereo display system, called StereoMirror, based on a digital display controller card and a pair of their C5i LCD medical grayscale monitors. They demonstrated a prototype of the new stereo display to Dr's Getty, D'Orsi and Karellas at the RSNA meeting in December, 2003. There was agreement of all involved that the new display seemed likely to meet the needs of the stereo mammography project if it could be developed and two systems built for BBN and Emory within a matter of months. Planar kindly agreed to do this and installed the first version of the stereo display system at BBN on March 31, 2004.

The prototype medical stereo display, the StereoMirror SD2250, developed by Planar Systems Inc. (1) is shown below in Figure 2. This stereo display consists of two 5 megapixel, grayscale monitors mounted one above the other with an angular separation of 110 degrees between the two faces. The two images, each displayed on one of the two monitors, are cross-polarized. A glass plate with a half-silvered coating (with 50% transmittance and 50% reflectance) is placed between the two monitor faces, bisecting the angle between them. The image presented on the lower (vertical) monitor is transmitted through the glass plate, while the image presented on the upper (angled) monitor is reflected from the top surface of the glass plate. The radiologist wears lightweight passive cross-polarized glasses with the result that the left eye sees only the reflected image from the upper monitor, while the right eye sees only the transmitted image from the lower monitor. The radiologist's visual system fuses the two images into a single in-depth image of the internal structure of the breast.

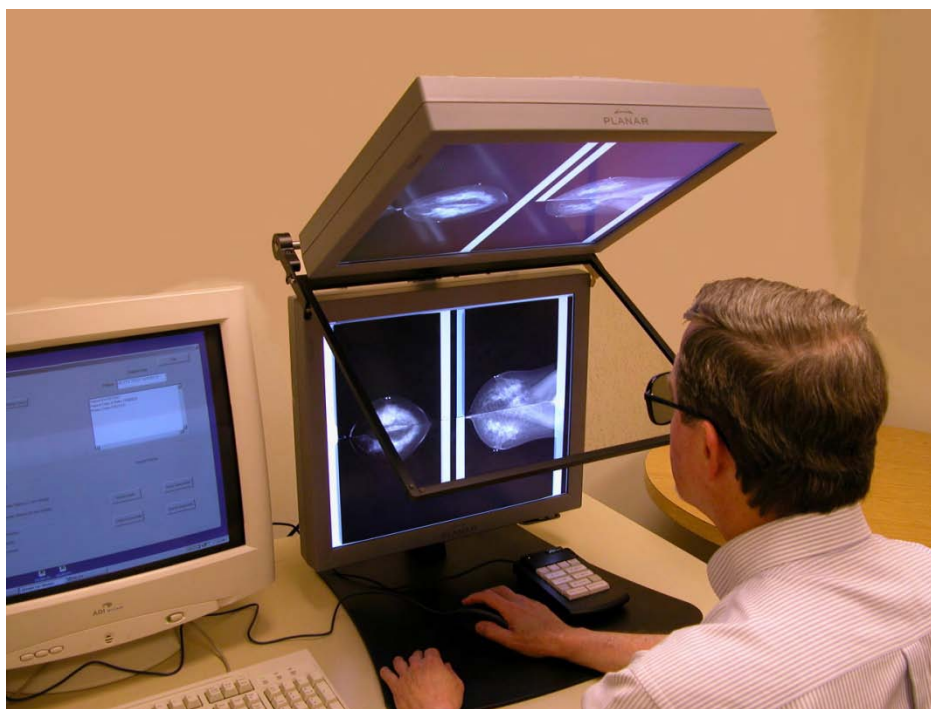


Figure 2. Planar StereoMirror stereo display system.

There are several advantages to the StereoMirror technology compared to the earlier CRT technology. First, the LCD monitors have a much brighter luminance level (~ 700 cd/m²) compared to the CRT (~ 150 cd/m²). Dr. D'Orsi considers this increased image luminance important in digital mammography. Secondly, for the LCD display, each image is seen *continuously* by the appropriate eye, whereas for the CRT display each eye sees the image only half the time due to the temporal alternation methodology. The latter results in a halving of the perceived image luminance, making the luminance difference between the two technologies even larger. Also, the new digital display controller card has improved capabilities that allowed us to develop a software magnifying glass that a mammographer could apply to regions of the mammographic image, and an in-depth cursor that the mammographer could move anywhere in the displayed tissue volume to point out objects to other viewers. These capabilities could not be implemented with the original analog display controller card because of its limitations.

1.3. Installation of the new stereo display workstation at Emory

In late August, 2004, Drs. Getty and Pickett traveled to Emory University to oversee the installation of the second copy of the stereo display workstation in the Emory Breast Clinic. The workstation included the new dual-LCD-based Planar StereoMirror stereo display developed in the prior year. Planar engineering personnel were present to assemble and align the components of the stereo display.

Drs. Getty and Pickett held training sessions with the five participating Emory mammographers and research staff to educate them in the use of the SDM Viewer software application for interactive viewing and control of stereo mammograms on the workstation.

2. Task 2: Refinement of the stereoscopic digital mammography display workstation

During Year 3 of the project, we made four refinements to the Stereo Viewer software, used by the mammographer to control the stereo display workstation. Also, we developed a program to anonymize the stereo mammographic images and transmit each case's images over the internet to BBN. We describe each of these refinements next.

2.1 Changing the base directory for viewing cases

The first refinement was to add a capability for the user to choose a different base directory from which to choose stereo mammography cases for viewing (the default directory is "C:\SDM Cases"). This enhancement permits definition of special subsets of cases for viewing, and is also convenient for testing purposes with special test images. The selection of a different base directory is made using the window shown in the upper left of Figure 3.

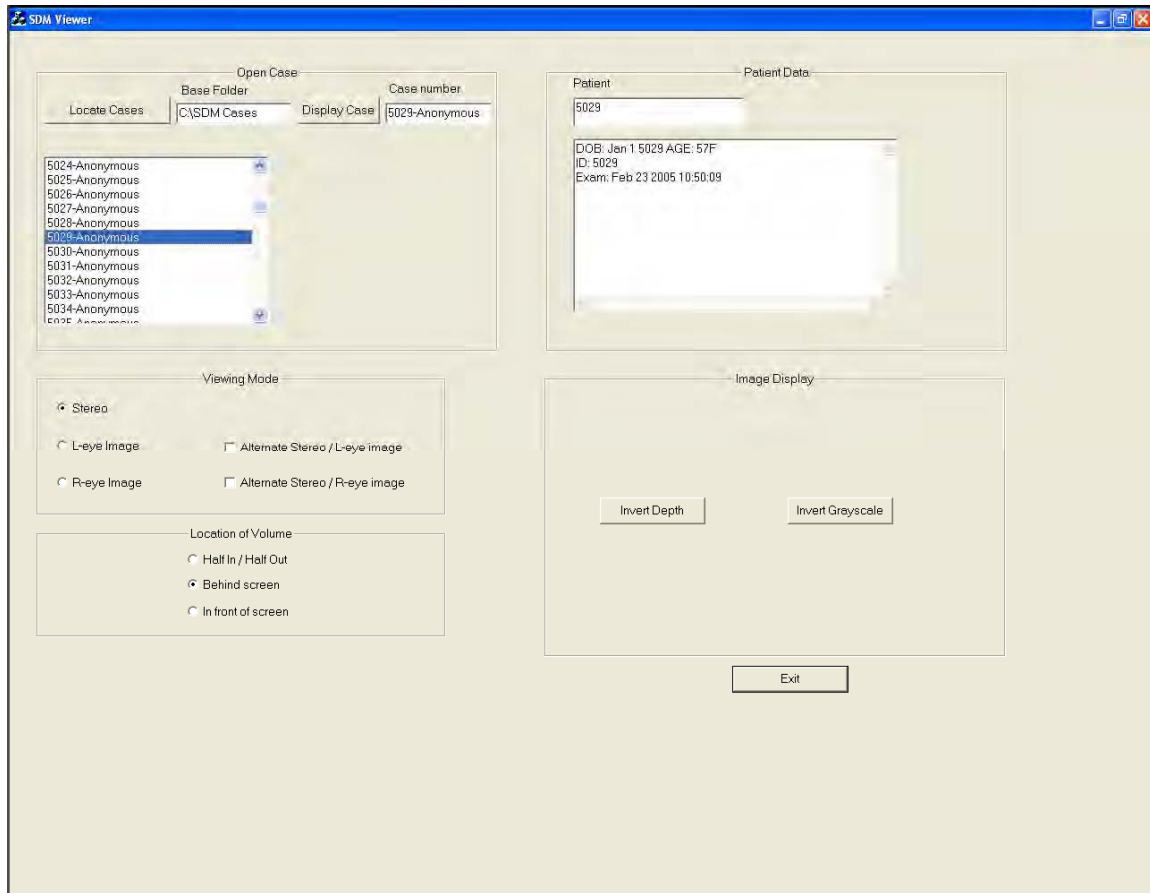


Figure 3. Control window of the SDM Viewer software application.

2.2 Changing the location of the displayed volume

The second refinement was to add a third possible location for the displayed volume relative to the display screen surface—“half in / half out”. In this display mode, the displayed volume is bisected by the screen surface, so that the front half of the volume lies in front of the display screen while the rear half lies behind the screen surface. The effect of this location of the stereo volume is that the absolute magnitude of the experienced parallax in the stereo image is half as large as that experienced with either the full in or full out modes of display. The possible disadvantage of this method of display is that the visual system experiences both crossed parallax (for portions of the image perceived to lie in front of the screen) and uncrossed parallax (for portions of the image perceived to lie behind the screen) within the same image. We initially set the default viewing mode to be this new mode, “half-in / half-out”. But, as the mammographers gained experience in viewing stereo mammograms throughout this past year, it appeared that they preferred, for reasons of visual comfort, to view the display volume as lying entirely behind the screen. As a result, we changed this to be the new default. However, a mammographer may freely set the viewing mode to any of the three options by clicking on the appropriate radio button, shown in the lower left of Figure 3.

2.3 Display of single-breasted patient images

The third refinement to the SDM Viewer was necessitated by the fact that some patients enrolled in the study had previously had a breast removed in a mastectomy. For these patients, the case images consisted only of CC and MLO stereo views of a single breast. The software was modified to check for the presence of images for only a single breast and, for such a case, to determine which breast was imaged and which was missing. The image panels in the Overview stereo image for the missing breast were left blank, and the corresponding keypad keys to display single views at full resolution were disabled.

2.4 Equalizing the grayscale histogram of the two images of a stereo pair

The fourth refinement, a highly significant one, was required to solve a problem resulting from the fact that there is independent control of each x-ray exposure on the GE Senographe digital mammography unit used to acquire the stereo mammograms in our study. The GE unit determines the exposure parameters for each x-ray acquisition from a brief pre-exposure through the central portion of the breast. The two images of a stereo pair are acquired while the breast remains compressed and fixed in place. The point of view of the breast is changed by a 10-degree rotation of the x-ray tube between the two exposures. Most of the time, this small change in point of view results in only very minor changes in the exposure parameters determined by the GE unit. However, occasionally, the two exposures differ significantly, in spite of the small change in the point of view of the breast. The result is that the grayscale histograms for the two images, while typically identical in shape, are shifted apart. The effect of this in the stereo display is that the two images of the stereo pair have different brightness, making stereo fusion of the pair difficult or impossible.

We were able to solve the problem, as follows. Following an exposure, the GE unit effectively computes the grayscale histogram of the image and stores a measure closely related to the grayscale mean for the breast tissue in the DICOM header. We decided on a new, desired grayscale mean that we wanted all images to share, and used the difference between each stored mean and the desired mean to correct the pixel grayscale values of each image. Thus, after correction, each case image had the same, constant grayscale mean. This solution not only equated the brightness of stereo image pairs suffering this problem, but also had the helpful side effect of equating the brightness of all stereo views for a case since all images are being corrected to exactly the same grayscale mean. In particular, this improves the appearance of the Overview image in which all 4 views (CC and MLO views of each breast) are displayed together in a single stereo image at half spatial resolution.

2.5 Anonymizing and transmitting stereo case images over the internet

We developed the means to transfer the stereo case images from the acquiring GE Senographe digital mammography unit directly to the stereo display workstation for viewing there. We also developed software to anonymize the DICOM file headers of a given case's images, ZIP the images into a single file, and then transmit the anonymized case over the internet to BBN for quality assurance testing and archival storage.

3. Task 3: Preparation of forms and a database for storing information on cases and readings

We wrote and refined a Research Protocol (Appendix A) and a Subject Consent Form (Appendix B) during the first two years of the project. Both documents were approved by the Emory IRB and by the corresponding Army review board, and renewed annually by the Emory IRB.

We also developed 6 forms that were used to collect data on each case: (1) a Clinical History form (Form CH), (2) a standard reading form (Form A1), (3) a stereo reading form (Form A2), (4) a consensus meeting resolution form (Form B), (5) a work-up examination results form (Form C), and (6) a biopsy results form (Form D). We describe these forms below. Copies of the final versions of the forms used in the project are included as Appendices C-H.

3.1 Standard and Stereo Reading forms (Forms A1 and A2)

These forms (Appendices C and D) were developed and improved during Years 1 and 2, prior to their use, to increase the useful information collected in each reading. Improvements included determining whether prior mammographic films were present during the reading, and a categorical assessment of the glandular tissue composition of the imaged breast(s). We also modified the finding-localization diagrams to resemble the presentation seen in the mammographic images.

For each identified finding requiring work-up, we added: (1) a rating of the finding's conspicuity, on a 10-point scale, (2) the BI-RADS category assigned to the finding, and (3) the recommended work-up actions for the finding.

We also added a section to the form permitting the mammographer to identify the type and location of benign findings seen in the images. Finally, we added an item for the BI-RADS category assignment *for the case*, considering all identified findings, and also added a space for comments.

3.2 Consensus meeting resolution form (Form B)

If one or more findings were reported either in the standard reading or in the stereo reading, or in both, then the two mammographers who conducted those readings met to compare the standard and stereo images with regard to those findings, reporting the results of their meeting on Form B (Appendix E). The first section of the form was used to establish the correspondence between findings detected in each reading, or to establish that a particular finding detected in one reading modality was *not detected* in the other reading modality. For each finding, the basis for any discrepancy was determined. The location of each finding was indicated on a breast diagram, and joint recommendations were made for work-up examinations.

3.3 Work-up results form (Form C)

For each finding identified in the consensus meeting as requiring work-up, the work-up results form (Appendix F) captures the results of all work-up examinations that were performed. Each examination result is indicated by a lesion-type code or a no-finding code. Finally, the mammographer conducting the work-up examinations assigns, for each finding, a final summary work-up code and BI-RADS category, estimates the likelihood of malignancy, and indicates whether biopsy is required.

3.4 Biopsy results form (Form D)

The biopsy results form (Appendix G) captures the pathology analysis results of each finding that was biopsied. Pathology of a finding is indicated by one or more codes indicating different types of benign and malignant disease. In addition, the form records the type of biopsy performed (percutaneous or excision) and whether the biopsied lesion was benign or malignant.

3.5. Project database and data entry scripts

Case data were entered into a database designed and maintained within the SPSS statistical analysis package. A total of 284 variables were defined within the database, derived from the patient's clinical history form, and the study data forms A-D. For a typical case, only a relatively small fraction of these variables were used. In order to streamline the data entry process, SPSS scripts were written that present the person entering the data with a series of electronic screens that are facsimiles of the hardcopy study forms. These are shown below for an illustrative, imaginary case.

After entering the study case number and indicating whether this is a new or existing (partially entered) case (Figure 4), the data entry person was presented with a screen permitting selection of the study forms to be entered (Figure 5). For new cases, the Clinical History form, and the Standard and Stereo Reading forms were pre-selected by default. By way of illustration, we show filled-out data entry screens for an imaginary new patient, study number 5357.

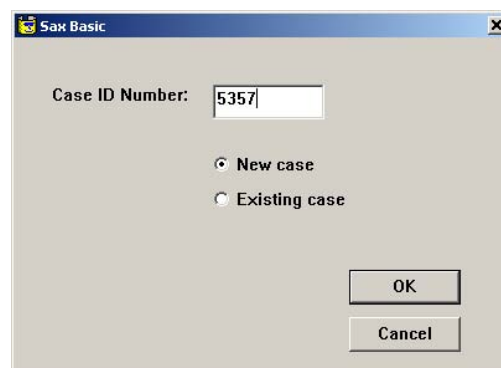
The image shows a screenshot of a software window titled "Sax Basic". Inside the window, there is a label "Case ID Number:" followed by a text input field containing the number "5357". Below the input field, there are two radio button options: "New case" (which is selected) and "Existing case". At the bottom right of the window, there are two buttons: "OK" and "Cancel".

Figure 4. Study case ID number screen.

In our example, this patient has findings detected both in the standard and stereo readings, which lead to further work-up examinations, and, ultimately on to biopsy. Consequently, all

study data forms are shown as checked off on the “Forms to be Entered” screen, shown below in Figure 5.

Figure 5. Forms to be entered screen.

For a new case such as this, the first data entry screen presented is the Clinical History screen, shown below in Figure 6. Here we see that this patient is 74 years old, has had both breasts imaged in this study, has several close female relatives who have had breast cancer, has previously had breast cancer herself in the Right breast, for which she received a lumpectomy, radiation therapy, and chemotherapy.

Figure 6. Clinical history entry screen.

The next data entry screen presented was the Standard Reading form (A1), shown below in Figure 7. It captures the dates of imaging and reading, the reader's initials, whether prior films were present at the reading, a general measure of breast density, and the number of findings, if any, in each breast. In this case, a mass is reported in the left breast and architectural distortion in the right breast. For each lesion, we record its location, the reader's confidence that the lesion really exists, the conspicuity of the lesion, the reader's estimate of the probability of malignancy, the BI-RADS category assigned to the lesion, and the recommended work-up examinations to be performed.

The reader was also asked to check off all benign findings seen in either breast, assign a BI-RADS category for the case, considering all findings: 0 (requires work-up), 1 (normal case), or 2 (clear or known benign findings). Space was left for any comments the reader might wish to leave.

Figure 7. Standard reading data entry screen.

The next data entry screen, shown in Figure 8 below, corresponds to the Stereo Reading form (A2) and captures exactly the same set of information as in the standard reading. The stereo reading is completely independent of the standard reading, and is carried out by a different reader. Over the course of the study, each reader read approximately equal numbers of cases in the standard reading condition and in the stereo reading condition.

In our illustrative case, the stereo reader has detected a single finding, a mass in the Left breast, but no finding in the Right breast.

Sax Basic
SDM DATA FORM A2 - STEREO READING

PATIENT STUDY NUMBER: 5357

DATE OF EXAM: 7/15/05

DATE OF READING: 7/16/05

READER'S INITIALS: mn

1. Prior films present? ☒ Yes ☐ No

2. Breast composition: ☐ Fatty ☐ Scattered densities ☒ Heterogen. dense ☐ Extremely dense

3. Number findings in each breast: LEFT: 1 RIGHT: 0

FINDING	Code	Side	Loc.	Conf. Real	Conspic.	Prob Malign	Birads	Spot	Mag	Roll	90	Exag	US	Other
1.	m	L	uo	90	9	25	0	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
2.								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
3.								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
4.								<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

BENIGN FINDINGS

	Mass	Benign c's	Unchanged c's	Rad therapy	IM nodes	Needle biopsy	Excision	Unchanged asym	Other:	
	R	L	R	L	R	L	R	L	R	L
UO	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
UI	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
LI	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
LO	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Case BIRADS: 0

Comments:

OK Cancel

Figure 8. Stereo reading data entry screen.

If either the standard or stereo reading, or both, resulted in detection of one or more findings, then the two readers met to review and compare the standard and stereo images in order to understand and resolve the differences, if any, in their respective findings. The results were captured on the Consensus Resolution of Findings form (Form B) and entered on the Consensus data entry screen, shown below in Figure 9.

First, the two readers agreed on the correspondence between findings seen in the standard reading and findings seen in the stereo reading, arriving at a total number of distinct findings. In our illustration, the mass seen in the Left breast by the standard reader is the same mass seen and reported by the stereo reader, as indicated by Finding 1 in Figure 9. However, the architectural distortion reported by the standard reader in the Right breast (Finding 2) was not reported by the stereo reader (indicated by the Stereo Code 0). The two readers make new recommendations about work-up exams to be performed on each finding.

Sax Basic X

SDM DATA FORM B - CONSENSUS RESOLUTION OF FINDINGS

PATIENT STUDY NUMBER: 5357

DATE OF CONSENSUS MEETING: 7/16/05

Total Number of findings (both breasts): 2

FINDING	Std. Code	Stereo Code	Side	Loc.	Basis	Spot	Mag	Roll	90	Exag	US	Other
1.	m	m	l	uo	0	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
2.	a	0	r	li	i	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
3.						<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
4.						<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Case BIRADS: 0

Comments: Architectural distortion seen in standard images appears to be superimposed tissue in the stereo images.

OK Cancel

Figure 9. Consensus resolution of findings data entry screen.

The results of the work-up examinations were recorded on the Work-up Results study form (Form C), and captured by the Work-up data entry screen, shown in Figure 10 below. For each distinct finding identified in the consensus meeting, the outcome of each work-up exam performed was recorded by the type of lesion identified, or by “0” if no lesion was detected.

In our illustrative case, the mass in the Left breast is confirmed in several different types of work-up exam (including a solid mass detected by ultrasound). This lesion is categorized as BI-RADS 5, signifying that it is probably malignant and must be biopsied. On the other hand, the architectural distortion reported in the standard reading in the Right breast, is not found on any of several work-up examinations. In the standard reading, the case was assigned as BI-RADS 0 (requiring work-up) and, thus, it was a *false positive* detection.

Sax Basic X

SDM DATA FORM C - WORK-UP RESULTS

PATIENT STUDY NUMBER: 5357

DATE OF WORK-UP: 7/20/05

DATE OF READING: 7/20/05

READER'S INITIALS: kg

Total Number findings: 2

FINDING	Standard	Stereo	Spot	Mag	Roll	90	Exag	US	Other-Type	Other-Result	Final Code	Prob Malign	Biopsy?	Birads
1.	m	m	m	m				sm			m	60	<input checked="" type="checkbox"/>	5
2.	a	0	0	0							0	0	<input type="checkbox"/>	1
3.													<input type="checkbox"/>	
4.													<input type="checkbox"/>	

Case BIRADS: 5

Comments

Figure 10. Work-up results data entry screen.

The final Biopsy data entry screen, shown below in Figure 11, was used to enter data from the Biopsy Results form (Form D). For each biopsied lesion, the nature of the biopsy (percutaneous or excision), the classification as Benign or Malignant, and the assignment of one or more pathology codes from a list were recorded.

In this case, a percutaneous biopsy of the mass was performed and it was found to be malignant. The lesion was coded as invasive ductal carcinoma and ductal carcinoma in situ.

PATIENT STUDY NUMBER: 5357

SDM DATA FORM D - BIOPSY RESULTS

DATE OF BIOPSY: 7/22/05

PATHOLOGIST'S INITIALS: dk

Total Number Findings: 1

FINDING	Work-up Code	Biopsy Type	Malig/Benign	Path Code 1	Path Code 2	Path Code 3	Path Code 4	Path Code 5
1.	m	<input checked="" type="radio"/> Percutan <input type="radio"/> Excision	<input type="radio"/> Benign <input checked="" type="radio"/> Malignant	idc	ds			
2.		<input checked="" type="radio"/> Percutan <input type="radio"/> Excision	<input type="radio"/> Benign <input type="radio"/> Malignant					
3.		<input checked="" type="radio"/> Percutan <input type="radio"/> Excision	<input type="radio"/> Benign <input type="radio"/> Malignant					
4.		<input checked="" type="radio"/> Percutan <input type="radio"/> Excision	<input type="radio"/> Benign <input type="radio"/> Malignant					

Comments

OK Cancel

Figure 11. Biopsy results data entry screen.

4. Task 4: Patient enrollment and acquisition of standard and stereoscopic digital mammograms

4.1 Patient enrollment

A total of 1458 patients were eligible and enrolled in the clinical trial at the Emory University Breast Clinic between January, 2005 and December, 2007, as shown below in Figure 12.

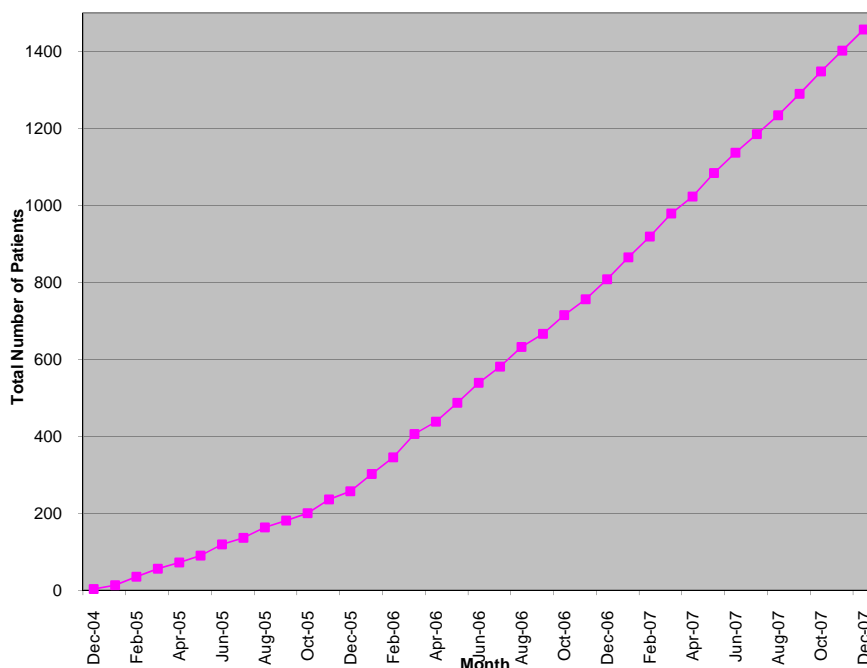


Figure 12. Cumulative enrollment of patients into the clinical trial.

Written informed consent was obtained from each patient. Only female patients were eligible for enrollment, and then only if they were at elevated risk for the development of breast cancer. Our reasons for using elevated risk as a criterion for inclusion were to maximize the number of lesions and cancers detected in the study and to provide reasonable justification for the additional x-ray exposure the patients received. Qualifying personal and family history risk factors included the following:

Personal risk factors:
(any of the following)

- Personal history of breast and/or ovarian cancer, regardless of age.
- Prior breast biopsy that included any of the following high risk, benign lesions, regardless of age:
 - Lobular carcinoma in-situ
 - Atypical lobular hyperplasia
 - Atypical ductal hyperplasia
 - Atypical columnar hyperplasia
- Positive test for known mutations on BRCA 1 or 2 genes, regardless of age.
- History of chest irradiation for treatment of non-breast disease at least 15 years prior to enrollment.

Family history:

(over 30 years of age with any of the following)

- Ashkenazi Jewish ancestry, regardless of age.
- Any history of male breast cancer on the maternal or paternal side.
- Breast and ovarian cancer in a close relative (mother, sister, daughter)
- Breast or ovarian cancer in more than one close relative (mother, sister, daughter)
- Breast cancer in a close relative (mother, sister, daughter) with early onset (<50 years of age)
- Breast and ovarian cancer in a 2nd degree relative (grandmother, aunt, niece) with early onset of breast cancer (<50 years of age).
- Multiple history of breast cancer in 1st and 2nd degree relatives.

4.2 Patient demographics

Of the 1458 patients, 864 (59.3%) had a history of prior breast cancer and 430 (29.5%) had undergone a single-breast mastectomy. The distribution of patients by age at the time of imaging is shown below in Figure 13. The mean patient age was 58.1 years, with a standard deviation of 11.6; the median patient age was 58 years. The youngest patient in the sample was 30 years old, while the oldest was 91.

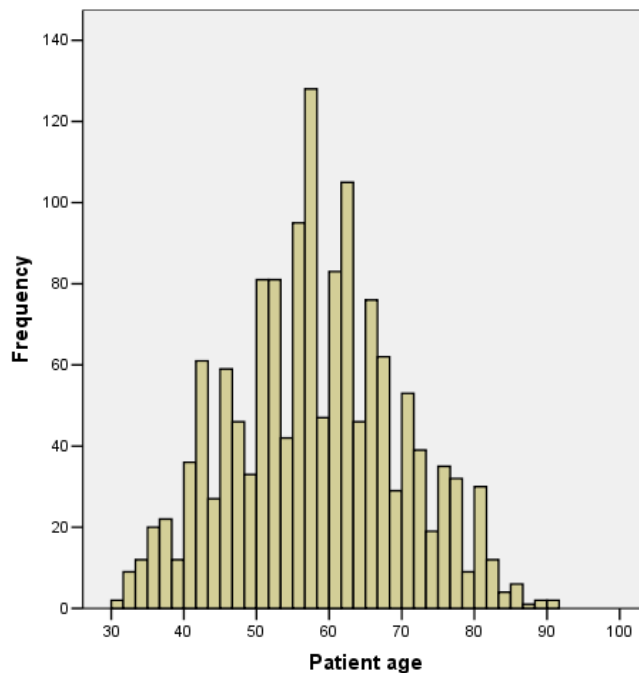


Figure 13. Distribution of patients by age at the time of imaging.

The distribution of patients by ethnic origin is shown in Table 1 below:

Ethnic Origin	Number of Patients	Percentage
Caucasian	1317	90.5%
African American	99	6.8%
Hispanic	17	1.2%
Native American	6	0.4%
Asian, Pacific Islander	7	0.5%
Other	9	0.6%

Table 1. Ethnic origin of patients in the clinical trial

4.3 Acquisition of standard and stereo mammograms

Each woman enrolled in the trial received both a standard digital mammographic screening examination and an independent stereoscopic digital mammographic screening examination in a single visit. The standard exam was performed using a clinical full-field digital mammography unit (GE Senographe 2000D). The stereo exam was performed on a research GE Senographe 2000D with modified x-ray collimation. Both exams consisted of the usual two views of each breast: cranio-caudal (CC) and medio-lateral-oblique (MLO) views. For the stereo exam, each of those two views was acquired as a stereo pair comprised of two images captured with the x-ray tube rotated by 10 degrees between the two acquisitions while the breast remained compressed and unmoved. Each image of a stereo pair was acquired with a standard x-ray dose.

5. Task 5: Reading of standard and stereo digital mammograms

5.1 Image display

The standard digital mammograms were viewed on a standard, FDA-approved, dual-monitor GE Review Workstation. The stereo mammograms were viewed on the prototype medical stereo display, the StereoMirror SD2250, developed by Planar Systems Inc. (1), described earlier.

We had developed software for the stereo display that permitted the radiologist to control many aspects of the displayed stereo images using a mouse and a small keypad. The radiologist could select a single stereo view for display at full resolution or, as shown in Figure 2, both stereo views of both breasts simultaneously at half-resolution. The radiologist could control brightness and contrast, reverse black and white, enable 2X image magnification with roaming, invert depth (reversing foreground and background), and enable a stereo cursor that could be moved in depth throughout the displayed volume. In addition, a control on the system monitor allowed the radiologist to choose the location of the displayed volume relative to the display screen surface—placing the volume entirely behind the screen, half behind and half in front, or entirely in front of the screen.

5.2 Readers

Five board-certified radiologists, all practicing mammography fulltime, participated in the clinical trial. A Randot Stereo Acuity Test (2) was administered to each mammographer to verify that he/she had functional depth perception and to measure his or her stereo depth discrimination acuity. The measurements showed that all five mammographers had excellent stereo depth acuity, discriminating objects in depth separated by no more than 30 seconds of arc of horizontal disparity in the stereo image.

As a control for individual differences, each of the five mammographers read approximately equal numbers of cases in the standard and stereo reading conditions. The percentage of the total number of cases read by each mammographer varied somewhat across the group, from a low of 13.8% to a high of 30.0%.

5.3 Image interpretation

The standard and stereo digital mammograms for each patient were read independently by two different radiologists as part of the daily clinical practice. Clinical histories were available to the radiologists for all enrolled patients, and prior mammograms were available for comparison for 99.0% of the patients. For each case, the radiologist filled out a form indicating the presence and nature of findings, if any, and the classification of the case using the BI-RADS assessment categories: 0 (recall patient for work-up), 1 (negative), 2 (benign), or, extremely rarely, 3 (probably benign). Categories 4 (biopsy suggested) and 5 (highly suggestive for malignancy) are not permitted at Emory for breast cancer screening. For each case, if both radiologists classified the case as BI-RADS 1, 2 or 3, no further action was taken. If either or both of the radiologists reported one or more findings requiring work-up (BI-RADS 0), then the two radiologists consulted to review both the standard and stereo images. If both had reported one or more findings, they sought then to determine the correspondence of findings between the two readings, and to concur on the nature of the requested work-up. However, all reported findings on stereo and/or standard mammography were recalled for work-up whether concordant or not. All patients with reported findings requiring recall received standard (non-stereo) clinical diagnostic work-up examinations. For each worked-up finding, a final BI-RADS assessment of category 1 was truth for absence of a lesion (i.e., a false positive), while a work-up assessment of categories 2, 3, 4, or 5 constituted truth that the finding of concern was a true lesion. Truth about the presence of cancer was determined from subsequent biopsy, if performed.

For each reported finding, the radiologist was also asked to rate the likelihood (on a scale from 0 to 100) that the finding would be confirmed at work-up as a true lesion. This measure was included to determine whether stereo mammography permitted a reader to more accurately judge that a finding being reported was a true lesion.

5.4 Statistical Analysis

The data were analyzed using SPSS software, version 13.0.1. All statistical tests reported in the Sensitivity and Specificity sections of the Results were conducted on two-by-two contingency table counts of standard and stereo outcomes using McNemar's test for correlated

proportions (3). These tests were two-sided, using exact methods. ROC analyses were performed using the ROCKIT software program, version 1.1B2 (4).

6. Task 6: Analysis of the reading data

Of the 1458 women enrolled in the trial, 282 (19.3%) were recalled for work-up of 332 reported findings. Standard mammography reported 216 findings while stereo mammography reported 176 findings; 60 of these findings were reported by both modalities. All of these patients were recalled and received standard diagnostic work-up exams. Of the 332 reported findings, 140 (42.2%) were shown at work-up to be true focal lesions (56 BI-RADS 2; 43 BI-RADS 3; 38 BI-RADS 4; 3 BI-RADS 5) while the remaining 192 (57.8%) were shown to be false positives (BI-RADS 1).

6.1 Sensitivity of lesion detection

Of the 140 true lesions, standard mammography detected 86 (61.4%), missing 54 (38.6%), while stereo mammography detected 106 (75.7%), missing 34 (24.3%) (Figure 14). Of these, 52 lesions were detected by both modalities. Thus, stereo mammography has increased true positive lesion detections by 23% and reduced false negative reports by 37 % ($p < 0.05$).

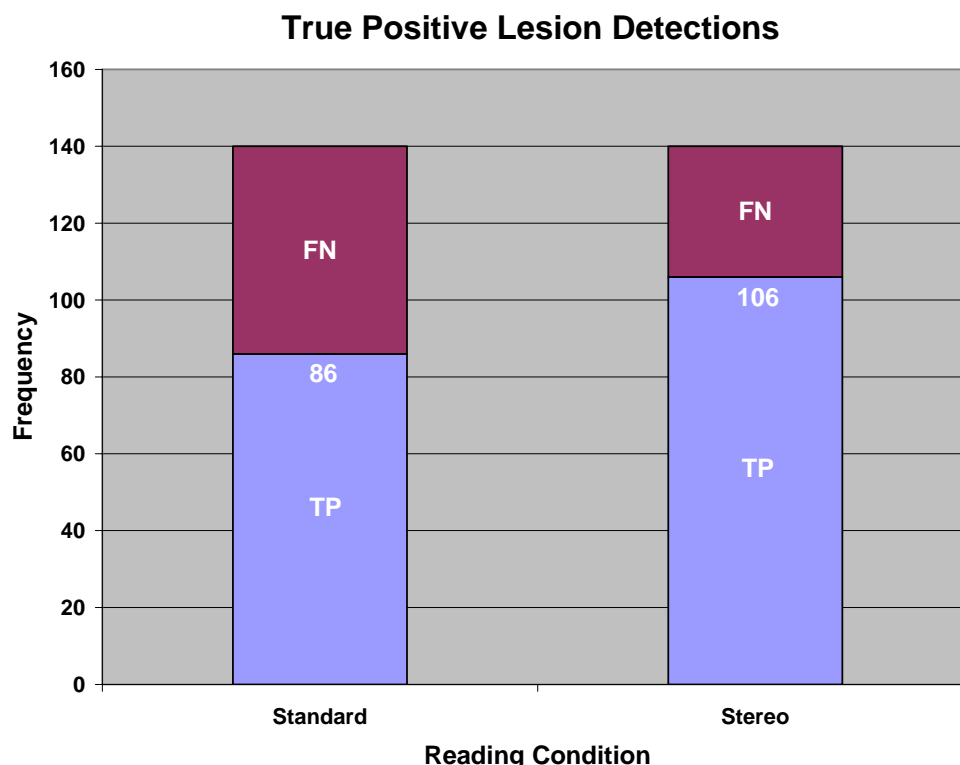


Figure 14. Frequency of true positive (TP) detections and false negative (FN) reports for findings shown to be true lesions at work-up.

Figure 15 shows the breakdown of true positive detections and false negative reports by type of lesion determined at diagnostic work-up. For clustered calcifications, stereo mammography detected 45 of the 50 calcification lesions while standard mammography detected only 22, a highly significant difference ($p < 0.003$). The differences between standard and stereo viewing for detection of other types of lesions (masses, architectural distortion and focal asymmetry) were small and none was statistically significant.

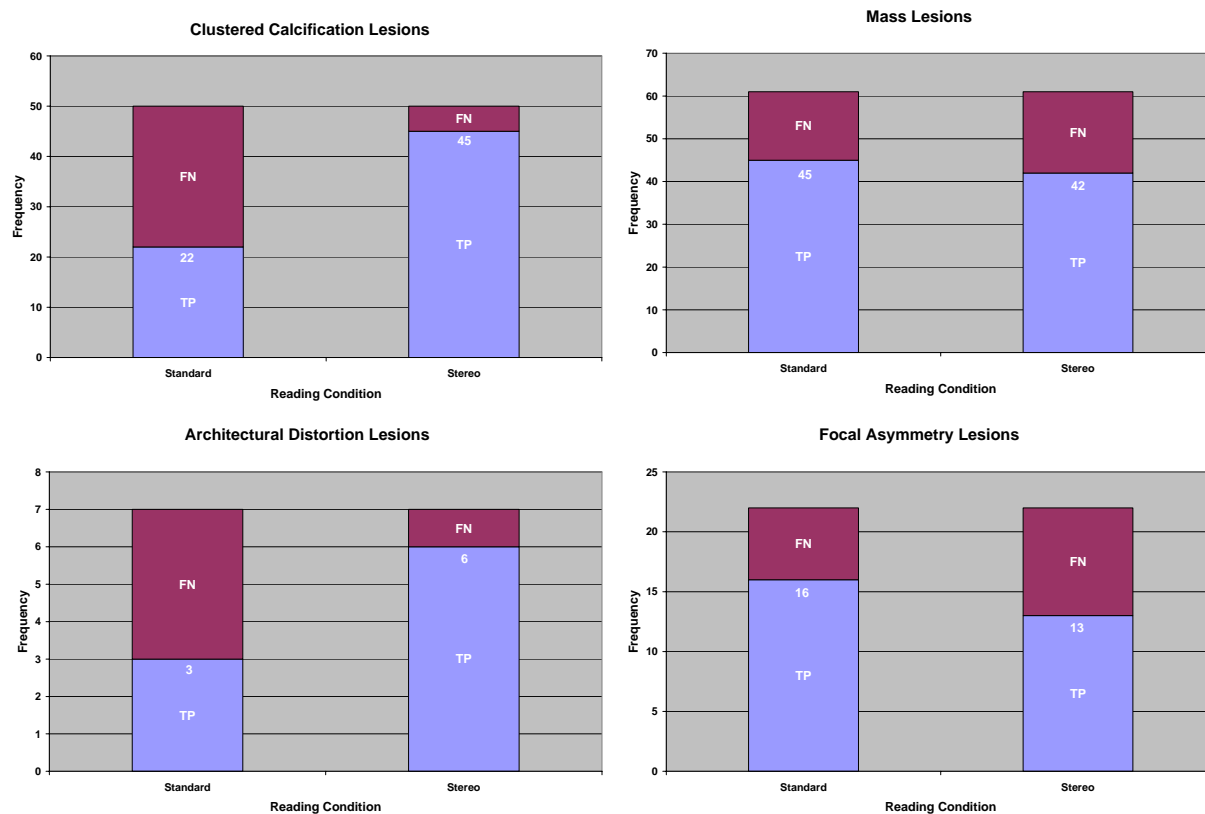


Figure 15. Frequency of true positive detections and false negative reports of lesions by type of lesion determined at diagnostic work-up.

Of the 41 lesions judged at work-up to be BI-RADS 4 or 5, 35 of the lesions were biopsied. At biopsy, 18 of the lesions were found to be benign while the other 17 (48.6%) were found to be malignant. Standard mammography and stereo mammography each detected 14 of the 17 malignancies (82.4%); 11 of the 17 (64.7%) were detected by both modalities, and each modality detected an additional 3 malignancies not detected by the other modality.

6.2 Specificity of Lesion Detection

As shown in Figure 16, of the 192 false positive detections, standard mammography was responsible for 130 (67.7%) while stereo mammography was responsible for 70 (36.5%), with 8 (4.2%) common to both. This 46% reduction in false positive reports with stereo mammography is highly statistically significant ($p < 0.0001$).

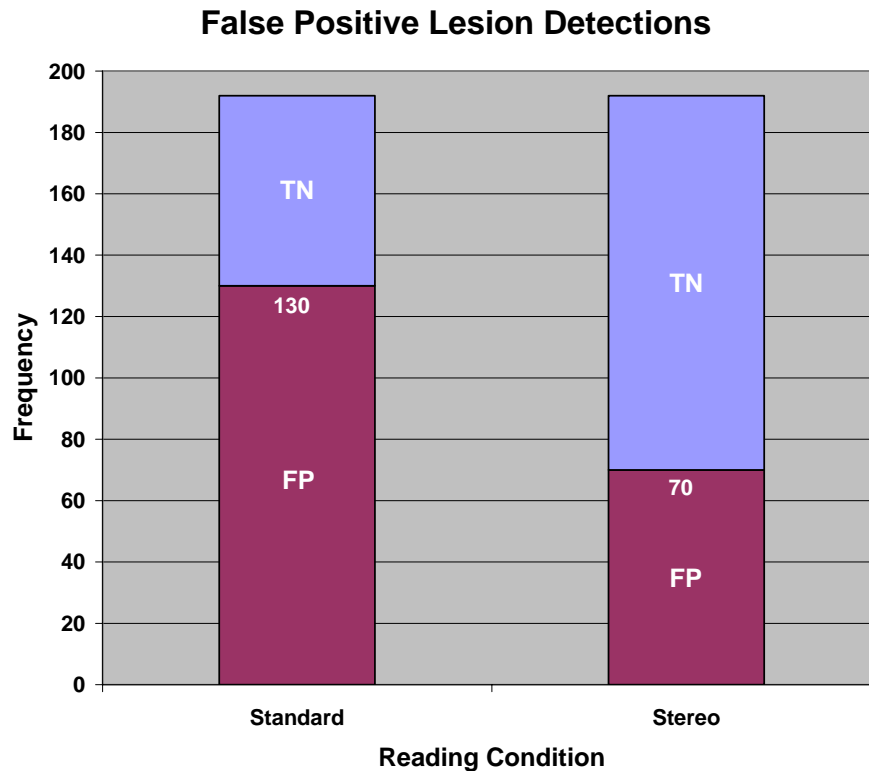


Figure 16. Frequency of false positive (FP) reported findings and true negative (TN) reports.

6.3 Likelihood that a Reported Finding is a True Lesion

An ROC analysis on the paired likelihood ratings for standard and stereo mammography was performed for the full set of cases. For cases where neither modality reported a finding, we set the likelihood of a true lesion to zero. For other cases in this set for which a finding was reported in one reading condition but not in the other, we set the likelihood that a finding would be confirmed as a true lesion to zero for the reading condition that reported no finding.

The empirical ROCs for the standard mammography and stereo mammography reading conditions are shown in Figure 17. We fitted correlated binormal ROCs to the likelihood ratings, and determined the area under the ROC, A_z , for standard mammography to be 0.85 and for stereo mammography to be 0.94, a difference in A_z that is highly statistically significant ($p=0.004$). The radiologists' judgments of the likelihood that a reported finding is a true lesion are more accurate with stereo mammography.

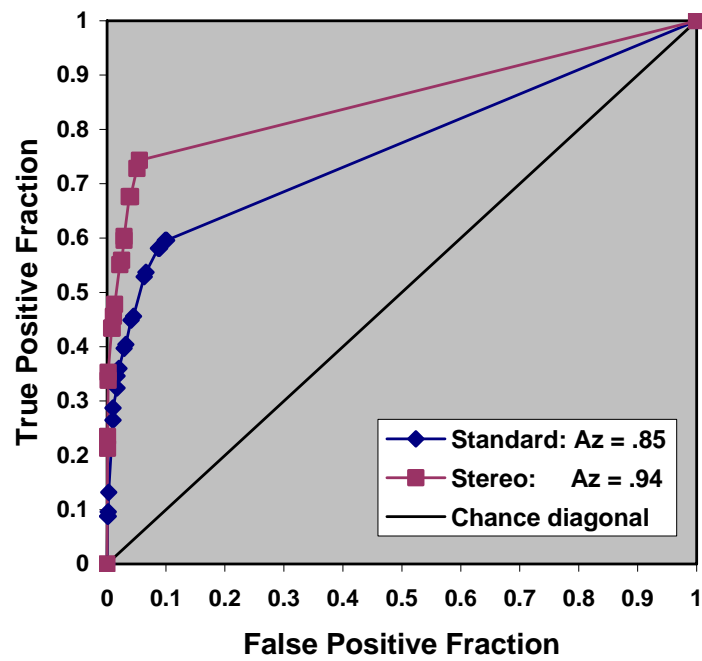


Figure 17. Empirical ROCs of the rated likelihood that a reported finding is a true lesion, for standard and stereo reading conditions.

KEY RESEARCH ACCOMPLISHMENTS

- Development and implementation of second and third generation stereoscopic digital mammography work stations.
- Development, testing and refinement of the user interface of the work station.
- Preparation of forms for organizing and collecting the image reading and truth data, and construction of a computerized data base for storing and eventual analysis of the study data.
- Recruitment and imaging with standard and stereoscopic digital mammography of the 1458 patients constituting the study sample.
- Independent reading of the standard and stereoscopic digital mammograms of each of the 1458 study patients, and obtaining work-up and biopsy data as needed.
- Analysis and interpretation of the study results and write-up for presentations and publication.

REPORTABLE OUTCOMES

AWARDS

2007 MITX (Massachusetts Innovation and Technology Exchange) Technology Awards. The Stereoscopic Digital Mammography research was honored to receive the first ever Societal Impact Award from MITX.

http://www.bbn.com/news_and_events/press_releases/2007_press_releases/pr_mitx_june_11

PRESENTATIONS

Getty, DJ. Stereoscopic digital mammography: perceptual and display factors leading to improved early detection of breast cancer. Presentation at *IWDM 2002, 6th International Workshop on Digital Mammography*.

Getty DJ. Stereoscopic and biplane digital radiography. Special Refresher Course presentation at the meetings of the Radiological Society of North America, Chicago, December 1-6, 2002.

Getty DJ. Stereoscopic and biplane digital radiography. Special Refresher Course presentation at the meetings of the Radiological Society of North America, Chicago, December 1-6, 2003.

Green P., Getty DJ. Stereoscopic digital mammography. Presentation regarding stereoscopic digital mammography, the Planar StereoMirror display, and the Emory clinical trial of stereo mammography to research and regulatory staff of the FDA. The purpose of the presentation was to acquaint the FDA with the stereo mammography technology, the scope of the clinical trial, and to begin preliminary discussions with them regarding steps needed to obtain future FDA approval for stereo mammography, 2004.

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Getty DJ, D'Orsi CJ, and Pickett RM. Stereoscopic digital mammography: Improved accuracy of lesion detection in breast cancer screening. Presentation at the 9th International Workshop on Digital Mammography, 2008.

PUBLICATIONS

Getty, DJ. Stereoscopic digital mammography: perceptual and display factors leading to improved early detection of breast cancer. In H-O Peitgen (Ed.), *Digital Mammography, IWDM 2002, 6th International Workshop on Digital Mammography*. Berlin: Springer, 2003, 431-435. (attached as Appendix H).

Getty, D. J. Stereoscopic and biplane digital radiography. In: E. Samei & M. Flynn (Eds.), *RSNA Categorical Course in Diagnostic Radiology Physics: Advances in Digital Radiography*. RSNA Publications, 2003, 199-209. (attached as Appendix I).

Getty DJ. Stereoscopic digital mammography. Proceedings of the First Americas Display Engineering and Applications Conference (ADEAC '04), Ft. Worth, 2004, 11-14. (attached as Appendix J).

Getty DJ and Green, PJ. Clinical medical applications for stereoscopic 3D displays. *Journal of the Society for Information Display*, 2007, 15: 377-384. (attached as Appendix K).

Getty DJ, D'Orsi CJ, and Pickett RM. Stereoscopic digital mammography: Improved accuracy of lesion detection in breast cancer screening. In EA Krupinski (Ed.), *Proceedings of the 9th International Workshop on Digital Mammography, IWDM 2008*. Berlin: Springer, 2008, 74-79. (attached as Appendix L).

PROJECT PERSONNEL

David J. Getty, Ph.D., P.I., BBN Technologies

Ronald M. Pickett, Ph.D., Investigator, BBN Technologies

Barbara Freeman, Research Associate, BBN Technologies

Carl J. D'Orsi, M.D., Co-P.I., Emory University

Ellen D'Orsi, Manager of Breast Research, Emory University

Mary Newell, M.D., Mammographer, Emory University

Kathleen Gundry, M.D., Mammographer, Emory University

Stephanie Roberson, M.D., Mammographer, Emory University

Sandra Bates, M.D., Mammographer, Emory University

CONCLUSIONS

The main findings of this project are that stereo mammography produced a statistically significant improvement over standard mammography in both sensitivity and specificity of lesion detection.

With regard to sensitivity, a question of considerable interest is how the gain in sensitivity overall was distributed among the lesion types. As shown in Figure 15, of the four types of lesion, only two, calcification clusters and masses occurred in sufficient numbers to support reliable analyses of difference between the two modalities. Those analyses show no apparent beneficial effect of stereo on the detection of masses, yet a strong beneficial effect on the detection of clustered calcifications. Indeed, almost all of the overall effect of stereo on sensitivity occurred with clustered calcifications. What accounts for this surprising asymmetry of effect deserves further study.

With regard to specificity, stereo mammography has reduced false positive detections by almost half compared to standard mammography. We believe that the large reduction in false positives is due to the fact that normal tissue, that would be superimposed in a 2D projection so as to resemble a focal lesion, is seen in the stereo mammogram as layers of normal tissue lying at different depths through the breast.

ROC analyses of the readers' ratings of confidence that the reported finding is a true lesion provide additional evidence of an increase in reading accuracy from stereo mammography. The area under the ROC curve (Figure 17) is significantly greater for stereo mammography, indicating that readers can make more accurate judgments with stereo about how likely it is that a finding they are reporting will turn out to be a true lesion at work-up. Although we did not record reading times, readers commented that they felt more confident in reading the stereo mammogram and that the reading required less time compared to reading the standard mammogram.

Though this study measured the impact of stereo on the detection of true lesions, not specifically malignant lesions, two implications of the findings for cancer screening are clear. The first is that stereo can be expected to reduce false positive recalls by as much as half. The second is that this large gain in specificity will not be purchased at a loss in sensitivity in the detection of cancer. To measure the exact effect of stereo on the detection of malignant lesions would require a much larger and longer-term study. But the present findings, showing a significant gain in the detection of true lesions, which would include malignant lesions in some proportion, suggest that there would almost certainly be at least a small gain in cancer detection as well.

If stereo, as implemented here, were ultimately applied as a replacement for standard mammography for screening, the required doubling of the x-ray dose would be unacceptable for routine screening. However, analysis of gains in signal detectability from binocular summation in the human visual system with stereo imaging (5,6) suggests that the per-image dose required for a fully adequate stereo image could be reduced to nearly one half of the standard dose, and that prediction has been confirmed in a recently reported reader study using mammography

phantoms (7). While this finding would have to be confirmed in a clinical setting, we expect that the effect of stereo with half-dose image pairs would be essentially the same as found here with full-dose image pairs.

It is also important to consider the role of stereo mammography in light of the ongoing development of both breast tomosynthesis (8-10) and dedicated breast CT (11-13), approaches to breast imaging which produce a slice-by-slice view of the breast volume. Like stereo mammography, these two new modalities are aimed at overcoming the problems of masking and mimicking of lesions associated with standard mammography. However, neither of these tomographic modalities, as currently read slice-by-slice, can provide direct visual experience of the volumetric structure within the breast. It remains to be seen whether either of the tomographic modalities will improve screening accuracy as much as stereo mammography is demonstrating here. Of additional interest are two potentially complementary roles of stereo and tomographic imaging. First, as hardware for tomosynthesis advances, it will provide platforms ideally suited for rapidly acquiring stereo image pairs because of the automated x-ray tube movement. Second, there is the possibility of providing the radiologist with stereo projections through all or a portion of the stack of reconstructed tomographic slices, all without any dose penalty, providing a potentially promising and practical approach to improved breast cancer screening.

Stereo mammography, by itself, could bring a substantial improvement over standard mammography in the accuracy of lesion detection and, with that, substantial gains in the cost-effectiveness of breast cancer screening. From improved sensitivity, it promises earlier cancer detection and saved lives. From improved specificity, it promises a substantial reduction in the number of false positives now sent by standard mammography for work-up, and with that, significant savings in both the emotional and financial costs of those procedures now incurred.

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APPENDICES

- Appendix A: Research Protocol
- Appendix B: Subject Consent form
- Appendix C: Standard reading form (Form A1)
- Appendix D: Stereo reading form (Form A2)
- Appendix E: Consensus meeting form (Form B)
- Appendix F: Work-up examination results form (Form C)
- Appendix G: Biopsy results form (Form D)
- Appendix H: Getty, DJ. Stereoscopic digital mammography: perceptual and display factors leading to improved early detection of breast cancer. In H-O Peitgen (Ed.), *Digital Mammography, IWDM 2002, 6th International Workshop on Digital Mammography*. Berlin: Springer, 2003, 431-435.
- Appendix I: Getty, D. J. Stereoscopic and biplane digital radiography. In: E. Samei & M. Flynn (Eds.), *RSNA Categorical Course in Diagnostic Radiology Physics: Advances in Digital Radiography*. RSNA Publications, 2003, 199-209.
- Appendix J: Getty DJ. Stereoscopic digital mammography. Proceedings of the First Americas Display Engineering and Applications Conference (ADEAC '04), Ft. Worth, 2004, 11-14.
- Appendix K: Getty DJ and Green, PJ. Clinical medical applications for stereoscopic 3D displays. *Journal of the Society for Information Display*, 2007, 15: 377-384.
- Appendix L: Getty DJ, D'Orsi CJ, and Pickett RM. Stereoscopic digital mammography: Improved accuracy of lesion detection in breast cancer screening. In EA Krupinski (Ed.), *Proceedings of the 9th International Workshop on Digital Mammography, IWDM 2008*. Berlin: Springer, 2008, 74-79.

Research Protocol

An Evaluation of Stereoscopic Digital Mammography for Earlier Detection of Breast Cancer and Reduced Rate of Recall

1. Investigators

Principal Investigator: David J. Getty, Ph.D.
Division Scientist
BBN Technologies
10 Moulton Street
Cambridge, MA 02138

Tel: 617-873-3751
Fax: 617-873-2794
Email: getty@bbn.com

Co-Investigators: Carl J. D'Orsi, M.D.
Director, Breast Imaging Center
Department of Radiology
The Emory Clinic
Emory University Hospital

Mary Newell, M.D.
Mammographer, Breast Imaging Center
Department of Radiology
The Emory Clinic
Emory University Hospital

Kathleen Gundry, M.D.
Mammographer, Breast Imaging Center
Department of Radiology
The Emory Clinic
Emory University Hospital

Stephanie Roberson, M.D.
Mammographer, Breast Imaging Center
Department of Radiology
The Emory Clinic
Emory University Hospital

Sandra Bates, MD
Mammographer, Breast Imaging Center
Department of Radiology
The Emory Clinic
Emory University Hospital

Ronald M. Pickett, Ph.D.
Professor of Psychology
University of Massachusetts – Lowell

Medical Monitor: Ernest V. Garcia, Ph.D.
Professor and Vice Chairman for Research
Department of Radiology
Emory University

Research Coordinator: Ellen D’Orsi, R.T. (R) (M
Manager, Breast Imaging Research
Emory University

Software Engineer: Prakash Manghwani, M.S.
Staff Engineer
BBN Technologies

2. Location of Study

BBN Technologies
10 Moulton Street
Cambridge, MA 02138

Primary Investigator: David J. Getty, Ph.D.
Division Scientist

Emory University Hospital
Breast Imaging Center
1701 Uppergate Drive
Suite C1104 WCI Bldg. 1st. flr.
Atlanta, Georgia 30322

Primary Investigator: Carl J. D’Orsi, M.D.
Director, Breast Imaging Center

3. Time Required to Complete

Expected start date: 01-August-2002
Expected completion date: 31-July-2007

4. Objectives

The primary goal of this project is to evaluate stereoscopic digital mammography, in a screening setting, for improved early detection of breast lesions, including breast cancer, and for reducing the rate of recall of patients for workup. We hypothesize that stereoscopic digital mammography, when compared with standard, non-stereo digital mammography, will:

1. Improve the detection of true focal breast abnormalities, including early breast cancer; and
2. Decrease the rate of recall of patients for further workup, by decreasing false positive readings without changing detection sensitivity.

There are three specific aims in this project. The first aim is to further develop the existing stereoscopic display system to improve its usability and efficiency for clinical use. We will observe radiologists using the stereo display and conduct interviews with them to determine ways to improve the human interface and to usefully augment its capabilities.

The second aim is to enroll approximately 500 women into the study in each of Years 2, 3, 4 and 5 of the project, for a total enrollment of about 2000 women. Women will be enrolled in the study only if they are at high risk for the development of breast cancer. Each woman will receive a screening exam consisting of a two view digital mammogram (a cranio-caudad and a medio-lateral oblique). In addition she will receive a two view stereoscopic exam consisting of two images per view (cranio-caudad and medio-lateral oblique) taken at slightly different angles.

The third aim is to conduct a controlled, paired study comparing stereoscopic digital mammography with non-stereo digital mammography for the detection of focal breast lesions and for the rate of recall for workup. Each case will be read independently by two different radiologists, one reading the stereo (research) mammograms and the other reading the non-stereo (routine clinical) mammograms. We note that we have chosen to compare stereo mammography with standard digital mammography rather than with film because it is the most direct and appropriate comparison. Support for this choice comes from a recently published study that concluded that there was no significant difference between digital mammography (using the same GE Senographe 2000D digital mammography unit that will be used in this project) and film in the rate of cancer detection.

5. Study Population

The target population for this study is women who are at high risk for the development of breast cancer. Approximately 8,800 women receive screening mammograms each year at the Emory Breast Imaging Clinic. Of these, about 10 percent, or approximately 880 women, are at high risk for development of breast cancer. We seek

to enroll approximately 500 of these women at high risk in this study during each of Years 2 through 5 of the project, for a total enrollment of about 2000 patients. A sample of this size is needed to detect a practically significant difference in the rate of lesion detection between stereo and non-stereo viewing. Our reasons for using high risk as a criterion for inclusion are: 1) to maximize the number of lesions and cancers detected in the study, and 2) to provide reasonable justification for the additional x-ray imaging the patients will receive. A high-risk patient who returns for yearly or accelerated screening examinations will be eligible for multiple enrollments in the study.

The protocol for this study will be very similar to that followed in the recently published project comparing full-field digital mammography with screen-film mammography for cancer detection in a screening population. We will use the following inclusion and exclusion criteria to determine eligibility:

Inclusion Criteria:

Personal risk factors (any of the following)

- Personal history of breast and/or ovarian cancer, regardless of age.
- Prior breast biopsy that included **any** of the following high risk, benign lesions, regardless of age:
 - Lobular carcinoma in-situ
 - Atypical lobular hyperplasia
 - Atypical ductal hyperplasia
 - Atypical columnar hyperplasia
- Positive test for known mutations of BRCA 1 or 2 genes, regardless of age.
- History of chest irradiation for treatment of non-breast disease (EX: lymphoma, lung cancer) at least 15 years prior to enrollment.

Family history (over 30 years of age with any of the following, some exceptions may apply)

- Ashkenazi Jewish ancestry, regardless of age.
- Any history of male breast cancer on the maternal or paternal side.
- Breast and ovarian cancer in a close relative (mother, sister, daughter)
- Breast or ovarian cancer in more than one close relative (mother, sister, daughter)
- Breast cancer in a close relative (mother, sister, daughter) with early onset (<50 years of age)
- Breast and ovarian cancer in a 2nd. degree relative (grandmother, aunt, niece) with early onset of breast cancer (<50 years of age).
- Multiple history of breast cancer in 1st. and 2nd. degree relatives.

Exclusion Criteria

- Patient does not meet any of the inclusion criteria,
- Patient has had breast augmentation, except for unilateral augmentation done for prior mastectomy,
- Patient has suspected or confirmed pregnancy,
- Patient has large breasts that cannot be adequately imaged on the 19 x 23 cm detector surface of the GE Senographe 2000D digital mammography unit.

6. **Protocol Design.** This project will use a prospective design in which each case will serve as its own control. The set of digital mammographic images acquired for a patient enrolled in the project will be used in both of the reading conditions being compared: stereoscopic reading of the two views of each breast versus non-stereoscopic, standard reading of the two views of each breast.

6a. Subject identification. The research coordinator or designee will access the already existing clinical history forms and prior mammography reports of patients scheduled for a screening mammogram. The research coordinator or designee will identify those patients who are at elevated risk, based on information on the forms and are candidates for recruitment into the study.

6b. Description of the recruitment process. The research coordinator or designee will call each scheduled patient that has been identified from the clinical history forms as being at elevated risk. The research coordinator will acknowledge and check the risk factors on the forms that are the basis of the elevated risk. It will be explained that, because of her elevated risk, she is eligible to participate in a study to evaluate a potentially better method for detecting breast cancer. The stereoscopic mammogram will be described briefly and the woman will be informed that the exam will take about 20 minutes more of her time when she comes for her routine screening mammogram and will include 4 extra mammographic images of each breast with compressions.

6c. Description of the informed consent process. Upon arrival for a scheduled mammogram, an eligible woman will be given a history questionnaire to complete. The patient will be asked if there is a chance of possible pregnancy and documentation of the patient's response will be noted on the history sheet. Possible pregnancy is an exclusion condition for the study and, in fact, for any screening mammogram. No pregnancy test will be administered. The consent form will be reviewed with the patient by the research coordinator or research technologist. At this time, any questions the woman has will be answered and, if need be, one of the radiologists involved in the study will also be available. Once both eligibility or exclusion criteria are determined and the patient agrees, two consent forms will be signed. One will be returned to the patient and the other will be kept for the study records. A copy will be made and put in the patient's medical record.

6d. Subject assignment. All of the patients enrolled in the study will be assigned for the standard digital mammogram first so a technique for the subsequent stereoscopic mammogram can be determined. Comparison of the two reading conditions being studied in the project (stereoscopic versus non-stereoscopic reading) will occur in the context of image interpretation by the radiologists.

6e. Subject screening procedures. Eligibility for admission to the study will be determined on the basis of written or verbal clinical history reviewed by the research coordinator or designee in advance of a scheduled screening mammogram.

6f. Data collection procedures. Each patient enrolled in the study will be assigned a sequential study ID number to protect patient identity. The study ID number will not include any personal identifiers (name, social security number, hospital ID number, date of birth). Only the PI of the project and the research coordinator or designee at Emory will hold master keys that relate the assigned study ID number to patient identity (name and hospital ID number). No personal identifying information will ever be disclosed in any reports or publication of this study. Four types of data will be collected on each patient enrolled in the study.

The first is the clinical history form that is part of the patient's medical record, and will be used to determine the patient's level of risk for development of breast cancer. A copy of the clinical history form will be stored in the project's research records, identified only by the subject's assigned study ID number.

The second data type is the set of standard (routine clinical) and stereoscopic (experimental) digital mammographic images. The routine clinical screening exam will consist of two views of each breast (cranio-caudad and medio-lateral oblique). The experimental stereo pair of images will be acquired by rotating the x-ray tube by approximately 10 degrees between images while the breast remains compressed. The first image will be acquired with the x-ray tube rotated clockwise by about 5 degrees from the zero angle position (perpendicular to the image receptor device) and the second image will be acquired with the x-ray tube rotated counter-clockwise by about 5 degrees from the zero angle position. A copy of the stereoscopic research digital mammographic images may also be transferred onto a CD-ROM or any other suitable electronic data storage device for transfer to the stereo mammography viewing station. The CD-ROM will be labeled on its top surface only with the assigned study ID number. Image files are identified on the CD only with sequential serial numbers (IM1, IM2...). No personal identifying information will be used in the filenames. After the radiologist's interpretation of a case at Emory, the CD-ROM may be sent to BBN for stereo image quality monitoring and for evaluation in making further improvements to the stereo imaging workstation.

The third data type are the two mammography BI-RADS report forms, one filled out electronically by the radiologist reading the standard non-stereo digital mammograms and the other filled out by the second radiologist reading the stereo mammograms. These will become part of the patient's medical record. A copy of these forms will be printed out

for the project's research records. These copies will be identified only by the assigned study ID number.

The fourth data type is a form filled out by the radiologist after completing the reading of a case in either the stereo or non-stereo reading condition. The radiologist will record on this form a quantitative judgment of the likelihood that a finding is a true focal abnormality, and a second judgment of the likelihood that a finding is cancer. This form will be identified only with the assigned study ID number.

All research records for the subjects will be kept in the research coordinator's locked office at Emory. A copy of the several study forms collected for each subject and the CD-ROM containing the stereo images will be sent to BBN, each identified only with the assigned study ID number. These mailings will be addressed directly to David Getty, the PI, and labeled as "Confidential." At BBN, the data will be entered into a computer database for analysis. The only identification of subjects in the database will be by the assigned study ID number. The CD-ROMs and research records will be kept in a locked office under the control of the PI. The computer database will reside in a password-protected computer in the PI's locked office.

The master key list linking the subjects' personal identification information with the assigned study ID codes will be kept in the Emory research coordinator's locked office, separate from all other study records and accessible only by the research coordinator.

The research and clinical mammographic images may be used by the investigators in scientific publications, posters, conferences and for teaching purposes. These images may also be given to other researchers within Emory University and at other establishments who may need them for scientific purposes. The clinical and experimental images may be displayed at scientific presentations that are open to the public and they may also be posted electronically on the worldwide web. However, all images that may be used for the above stated purposes will be completely de-identified and it will not be possible to trace the identity of any patient from any of these images.

Agencies that have a right to examine patient records collected in this study include the Emory Institutional Review Board, BBN Technologies, and the U.S. Food and Drug Administration. In addition, representatives of the U.S. Army Medical Research and Materiel Command are eligible to review research records as part of their responsibility to protect human subjects in research.

6g. Clinical assessments. The primary clinical assessment of the patient may come from the standard reading of the non-stereo digital mammograms and from the additional reading, by a different radiologist, of the stereo digital mammograms. Assignment of each participating radiologist to the two reading conditions will be counterbalanced across patients. The reading of the stereo mammograms will have the potential of contributing to the patient's current diagnosis if something is seen in the stereo mammogram that was not seen in the standard mammogram. Any finding, seen in either reading condition, will be acted upon as appropriate. The inclusion or exclusion of findings in the clinical report will be determined by the consensus of a periodic meeting

of both involved radiologists after the third and fourth data points are completed for each patient. Each patient will be called at about 18 months following stereo imaging to determine outcomes so as to score the contributions of stereo mammography to the accuracy and efficacy of diagnosis.

6h. Data analysis. Truth for each reported finding will be established from imaging workup, biopsy results or 18-month follow-up. Two types of truth will be determined. First, we will determine *lesion truth*: whether or not the reported finding is a true focal abnormality. Lesion truth will be determined either from imaging workup (film studies using spot compression, magnification or other views, and/or ultrasound examination), follow-up examinations, or from biopsy results. Second, for each confirmed focal abnormality, we will determine *cancer truth*: whether the finding is malignant or benign. Cancer truth will be established either from a biopsy or from follow-up phone call 18 months after imaging. All cases, where a confirmed focal abnormality was not deemed worrisome enough to be sent to biopsy, will be followed at 18 months to confirm whether that focal abnormality was truly negative for cancer.

We will conduct several analyses of the collected data. First, using standard ROC methods, we will compare the performance of stereoscopic digital mammography to non-stereo digital mammography for detection of breast lesions. The set of confirmed lesions to be used in this, and other, analyses will be the union of all findings reported in either the stereo reading condition or the non-stereo reading condition, or in both. A finding that is reported in one reading condition, but not the other, will be scored as a zero on the rating scales (likelihood of a true lesion and likelihood of cancer) for the reading condition in which the finding was not reported. ROC curves will be fitted to the judgments made independently in each of the two reading conditions. We will compute A_z , the area under the ROC curve, as a measure of accuracy for each fitted ROC. Statistical analysis will be conducted on the difference between the A_z computed for each reading condition, using ROC methods that account for the correlation induced by the same case set being read in the two different conditions.

Similar ROC analyses will be applied to the judgments of the likelihood of cancer. Statistical analysis of the difference between the A_z 's computed for stereo digital mammography and non-stereo digital mammography will be completed to determine if there is a difference in the cancer detection rate.

We will examine the frequency of recommended recall of patients for further workup or biopsy based on the BI-RADS classifications (classifications of 0, 4 or 5) obtained from each reading condition. Statistical analysis of the difference in this frequency for the two conditions will be conducted on the 2 x 2 table of frequencies using chi-square tests. In a related analysis, we will also construct an ROC curve for each condition using the BI-RADS classifications as a rating scale, ordered by increasing suspicion of malignancy as 1 (negative), 2 (benign), 3 (probably benign), 0 (need additional imaging evaluation), 4 (suspicious abnormality), 5 (highly suggestive of malignancy). By statistically comparing the two fitted ROC curves, we will determine whether there is a difference between the stereo and non-stereo readings in the predictive accuracy of recalling a patient for workup or biopsy.

7. Risks/Benefits Assessment

7a. Risks. There is no additional risk of physical injury in acquiring the stereo mammogram beyond that associated with a standard mammogram. There is the minimal risk of physical injury in the normal procedure of positioning and taking a mammogram. A compression paddle will be used to flatten the breast to a uniform thickness for the images. There is the risk that some bruising could occur due to the compression; this is the same risk as for the routine mammogram.

As a result of this study, participants will be subjected to a small additional amount of radiation. A typical technique will be: 26 KVP, 100 mA, and one-second exposure. A higher mAs will be used for more dense breasts, but the technique used will be about the same as with conventional film-screen imaging. The kVp utilized may vary by about ± 3 kVp depending on the thickness of the breast; this is standard practice in mammography. The x-ray beam will be restricted to the general area of interest. The average glandular dose received by the breast from each mammographic x-ray view will be approximately 160 mrad. This is about the same radiation dose given to patients in routine film mammography. This dose is approximately half the maximum dose of 300 mrad (mean glandular) recommended by the American College of Radiology (ACR) for a single-view mammogram. The Total Body Effective Dose Equivalent per image will be 8 mrem, or 32 mrem total for the four extra images per breast specified by the experimental protocol.

As part of the routine mammographic examination, the patient will be interviewed by the x-ray technologist with regard to pregnancy. In current routine practice, premenopausal patients are asked whether they are pregnant, or trying to become pregnant. The majority of this group gives a negative response to this question, and mammography is performed in the usual manner. It should be noted that there is always a small theoretical probability that a woman in this group was pregnant and had both the standard and stereoscopic mammogram. Because of the very low energy of the x-ray beam, even in the case of the pregnancy, the dose to the fetus would be very close to the natural background radiation. Patients who are pregnant or trying to become pregnant will be excluded. As in routine mammography, we expect that most of the subjects will be beyond their childbearing years. Screening for pregnancy will be done only by asking questions and not by any blood or urine tests. It is also possible that additional evaluations which turn out to be negative or benign, may take place because of the addition of the stereoscopic mammogram.

7b. Benefits. An individual participant may directly benefit from the stereo mammography examination if additional information is detected in the reading of the stereo mammogram that is not seen in the standard, non-stereo reading. In this case, further workup of the patient would occur using standard, approved procedures. In general, however, this research project is not intended to directly benefit the individual participants. But, the information collected in this study may lead to significant improvements in the earlier detection of breast cancer through the use of stereoscopic digital mammography. The results of this research could eventually benefit all women undergoing mammography.

7c. Compensation. Subjects consenting to take part in this study will not receive any compensation for their participation.

7d. Voluntary Participation/Withdrawal. A subject's participation in this study is entirely voluntary. A woman who is invited to participate may decline without prejudice. Likewise, a subject who has enrolled in the study may choose to drop out at any time. The decision to decline enrollment or to drop out will have no effect on the woman's current or future medical care or any benefits to which she is otherwise entitled. If a woman drops out of the study, her study records will be excluded from all further review and analysis.

Under unusual circumstances, the investigator may choose to terminate an enrolled subject's participation in the study. Such circumstances might include equipment failure, discovery of an exclusion condition not evident at the time of enrollment, or development of a medical condition that precludes participation.

8. Reporting of Serious or Unexpected Adverse Events

Every patient will be carefully monitored and closely followed during the imaging procedure. Carl J. D'Orsi, M.D., FACR, will be monitoring all phases of the study as they apply to Emory University. Dr. D'Orsi will be actively involved in all aspects of this study and will be available to assist if any medical emergency should arise. Dr. Andrew Karellas is the Director of Radiologic Physics and will monitor all equipment as it applies to this study. Dr. Ernest Garcia, Ph.D. will serve as the medical monitor assigned to this study.

Adverse experiences that are both serious and unexpected will be immediately reported to the Emory University IRB and by telephone to the USAMRMC Deputy for Regulatory Compliance and Quality (301-619-2165) (non-duty hours call 301-619-2165 and send information by facsimile to 301-619-7803). A written report will follow the initial telephone call within 3 working days, sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

9. Disposition of Data

The digital mammographic images will be stored in the RADSTOR image archiving system, as part of the patient's medical record. The copy of the stereo digital mammograms written on a CD-ROM, and identified only by the assigned study ID number, will be retained at BBN throughout the duration of the project and for 3 years following.

The data forms, identified only by study ID, will be retained through the period of the project at both Emory University and BBN and may be destroyed at the study closure. However, the data contained on the forms will be transferred during the project to the database maintained at BBN. At termination of the project the database will be written onto CD-ROM. One copy of the database CD-ROM will be kept at BBN and another copy sent to Emory. There will be no personal identifying information in the database.

The master key list linking study ID numbers to subject personal identifiers will be kept at Emory University for 3 years beyond the termination of the project.

The database CD, mammographic images CDs, and the master key list may be destroyed 3 years after termination of the project.

10. Modification of the Protocol

Proposed modifications or amendments to the protocol will be submitted to the Emory IRB and to the HSRRB for review and approval prior to implementation.

11. Departure from the Protocol

Should any departure from the approved protocol be deemed necessary due to unforeseen events, the Emory IRB and the HSRRB will be notified of the nature of the deviation, the reasons for its occurrence, and the proposed remedy, if appropriate, for review and approval prior to implementation.

12. Roles and Responsibilities of Study Personnel

BBN Consultant

David J. Getty, Ph.D., is Division Scientist at BBN Technologies and will serve as Principal Investigator for the project. As PI, he will provide oversight of the ongoing activities of the project at BBN and at Emory University. He will have primary responsibility for the further development and refinement of the stereo display system that will take place at BBN. He will be responsible for overseeing the design of the electronic database, the design of data collection forms. He will have primary responsibility for carrying out planned analyses of the data comparing reading of the stereo mammograms with reading of the non-stereo mammograms. He will have primary responsibility for preparing the annual reports for the Army, and for presenting the results of the project at scientific meetings and in publications.

Prakash Manghwani, M.S. (Computer and Information Science), is a Staff Engineer at BBN. Mr. Manghwani is a highly experienced programmer who will be responsible for writing the software application that controls the stereoscopic display system. The goal of this effort is to develop an application that permits a radiologist to manipulate the appearance of a stereo mammogram in well human-factored ways that are powerful, convenient and efficient in a clinical setting. The application will be refined iteratively as we receive feedback from radiologists using the system over the course of the project.

BBN Consultant

Ronald M. Pickett, Ph.D., is a Professor of Psychology at the University of Massachusetts—Lowell. He has worked closely with Dr. Getty on related radiological imaging projects for the past 25 years. He is an expert on human visual perception experimental design, and ROC analysis methods. He will consult throughout the project in all of these areas: helping to improve the human factors of the stereo display system to maximize information provided to the radiologist, helping to design the reading study

comparing the stereo and non-stereo reading conditions, and helping in the choice of the methods of data analysis and result interpretation.

Emory University

Carl J. D’Orsi, M.D., is Director of the Breast Imaging Clinic at Emory University. He will serve as primary investigator of the clinical portion of the project conducted at Emory University, with responsibility for overseeing the enrollment of patients into the project, acquisition of stereoscopic digital mammograms on those patients, reading of the non-stereo and stereo mammograms by participating radiologists, and entry of the collected data into the electronic database. Dr. D’Orsi is a renowned radiologist with an international reputation in mammography. He has worked with Dr. Getty on medical projects for more than 20 years. He will also work with Dr. Getty in designing the data collection forms and database to be used in the project, and in the interpretation of the study results.

Mary Newell, M.D., is a radiologist, specializing in mammography, in the Breast Imaging Clinic at Emory University. She will serve as a reader of both the stereoscopic digital mammograms and the standard, non-stereo digital mammograms acquired in the project.

Kathleen Gundry, M.D., is a radiologist, specializing in mammography, in the Breast Imaging Clinic at Emory University. She will serve as a reader of both the stereoscopic digital mammograms and the standard, non-stereo digital mammograms acquired in the project.

Stephanie Roberson, M.D., is a radiologist, specializing in mammography in the Breast Imaging Clinic at Emory University Hospital. She will serve as a reader of both the stereoscopic digital mammograms and the non-stereo digital mammograms acquired in the study.

Ellen D’Orsi, R.T. (R) (M) is Manager of Breast Imaging Research at Emory University. She will be responsible for:

- Overseeing the recruitment process and for obtaining informed consent.
- Enter clinical history and radiologic reading data into the database.
- Assigning and maintaining the study ID numbers.
- Sending data and transmission of digital images to BBN.
- Insuring that studies are read according to the established time frame of 7 days.
- Facilitating appointments for additional imaging.
- Dealing with any concerns or complaints from study participants.

Andrew Karellas, Ph.D., is a professor of radiology and director of Medical Physics in the Department of Radiology at Emory. Dr. Karellas is an expert in the physical aspects of x-ray imaging with particular expertise in mammography. He will be responsible for the monitoring of the x-ray equipment that will be used in this project.

Ernest Garcia, Ph.D., is assigned the role of Medical Monitor for this project. He will be responsible for monitoring the care provided to enrolled patients, and arranging any necessary medical care to any enrolled patient who experiences any serious and unexpected event that occur as part of the study. He will review any such event and provide a written report within 3 calendar days of the initial report. This report will be forwarded to the USAMRMC.

**Emory University School of Medicine
Department of Radiology
Consent to be a Research Subject**

Title: An Evaluation of Stereoscopic Digital Mammography for Earlier Detection of Breast Cancer and Reduced Rate of Recall

Sponsor: Department of Defense Breast Cancer Research Program

Principal Investigator: Carl J. D'Orsi, MD

Co-Investigator: Mary Newell, MD
Kathleen Gundry, MD
Stephanie Roberson, MD
Sandra Bates, MD

Introduction/Purpose: You are being asked to take part in a research study. You have been asked because you are scheduled to have your annual screening mammogram and you are high risk for the development of breast cancer. This study will compare two different ways of doing a mammogram, a standard digital mammogram vs. a stereoscopic digital mammogram. Both these exams involve radiation (x-rays). The stereo mammogram enables the radiologist to see the breast tissue in depth, as a 3D image. It does require a very small amount of additional radiation. The digital mammogram is your standard screening method; it is not research. It is hoped that the stereo mammogram will reveal true, breast tumors at an earlier stage, and decrease the number of patients who have to come back for repeat mammograms when an abnormal area is seen at screening. You will not receive results from your standard mammogram today as a report cannot be issued until both exams are read and each exam will be read by a different radiologist, at different times. Taking part in this study will require about 20 minutes of your time today. About 5 minutes of that time will be answering some questions about your medical history. The total enrollment for this study is 2000 women, all to be done at Emory University Hospital's Breast Imaging Center.

Procedures: If you agree to take part in this study, your mammogram will be done by both methods at the same appointment. The routine digital mammogram will be done first. Your breasts will be positioned and compressed, one at a time on the mammography unit. The standard two views will be taken. You will then be moved to the research room for the stereoscopic research mammogram. You will be positioned and compressed in the same way as for the routine digital exam. Two views will be done on each breast just as before. The only difference is that there will be two exposures per view, for a total of four exposures per breast for the research mammogram. A radiologist will read the stereoscopic images at a specially de-signed stereo-display workstation while wearing stereo-viewing glasses. The reading of those images will be compared to the reading of the standard digital images, read previously by a different radiologist.

Your Doctor will receive a report based on all the available information. You will receive a letter or phone call from the Breast Imaging Center in approximately 7 business days concerning your results. If any abnormalities are found, you will be called back for further work-up. Should you need to have further work-up or an area biopsied (needle inserted and tissue taken out), we are asking your permission to review your medical records and test results. A copy of all reports and study forms will be kept in your chart in the research coordinator's office.

Risks: If you take part in this research, you will have a medical imaging study that uses radiation. The test you will have includes ordinary x-rays. To give you an idea about how much radiation you will receive, we will make a comparison with an every-day situation. Everyone receives a small amount of unavoidable radiation each year from the natural environment. Some of this radiation comes from space and some from naturally occurring radioactivity in the soil, food and air. For the average patient, this research procedure delivers to the body the equivalent of less than 3 extra months' worth of natural background radiation. The radiation dose we have discussed is what you will receive from this study only and does not include any exposure you may have received or will receive from other tests. Radiation exposure can potentially increase your chance of developing cancer. The risk is very small, and may even be zero for the radiation exposure from this study. Pregnant women may not participate in this study due to the possible risks of radiation exposure to the fetus. Since any findings, either on the routine digital mammogram or on the experimental digital stereoscopic mammogram may be evaluated, you could possibly have additional tests and/or breast biopsies that may not have happened if you did not participate in this study. There is the risk that some bruising could occur due to compression; this is the same risk as for the routine mammogram. There may be risks, discomforts and side effects that are yet unknown.

Benefits: Taking part in this research study may not benefit you personally, but we [doctors, researchers and scientists] may learn new things that will help others. It is also possible that a biopsy requested because of your participation in this study leads to detection of early breast cancer.

Alternatives: You may choose to not take part in this study and just have your standard screening mammogram.

Compensation and Cost: You will not be paid to take part in this study. Your standard digital mammogram and any additional follow-up will be billed to you or your insurance. There is no charge to you for the research stereoscopic mammogram. We will arrange for emergency care if you are injured by this research. However, Emory University has not set aside funds to pay for this care or to compensate you if a mishap occurs. Your insurance may be billed for any medical care provided by Emory University, but Emory will not bill you for research-related medical expenses that are not covered by insurance (for example, deductibles or co-pays), or for these expenses if you are uninsured.

You or your insurance companies are responsible for paying for any medical care provided by sources other than Emory University. You should also understand that this is not a waiver or release of your legal rights. If you believe you have been injured by this research, you should contact Carl J. D'Orsi, MD at 404-778-4446.

Voluntary Participation/Withdrawal: Your participation is completely voluntary and you have the right to refuse to be in this study. You can stop at anytime after giving your consent. This decision will not affect in any way your current or future medical care or any other benefits to which you are otherwise entitled. The study doctor/investigator and/or sponsor may stop you from taking part in this study at any time if they decide it is in your best interest, or if you do not follow study instructions.

Contact Persons: If you have any questions about this study or if you feel being in this study has harmed you, contact Carl J. D'Orsi, MD at 404-778-4446. If you have any questions or concerns about your rights as a participant in this research study, contact Colleen DiOrio, PhD, Chairman of the Emory Institutional Review Board at 404-727-5646.

New Findings: We may learn new things during the study that you may need to know. We can also learn about things that might make you want to stop participating in the study. If so, you will be notified about any new information.

Confidentiality (Protection) of Your Research Records: You will be assigned a study ID number that will be used on all study records. The study ID number will not include any personal identifiers, such as your name, social security number, medical record number, or date of birth. All study records at Emory will be kept in the Research Coordinator's locked office.

The study's Research Coordinator at Emory will keep a master list that links your identity to your assigned study ID number. This master list will be kept in a separate file in the Research Coordinator's locked office. The project's Principle Investigator at BBN Technologies will also keep a copy of this master list in a separate file in his locked office. Only the Emory Research Coordinator and designated Breast Imaging research staff and the Principle Investigator at BBN Technologies will have access to the master lists. The master list will be kept for at least 5 years after the termination of the study.

The data forms generated in this study and the stereoscopic mammographic images that will be stored on a CD-ROM will be identified only by your assigned study ID number. No personal identifiers will be used. Copies of these forms and the mammographic images will be sent to BBN Technologies for analysis, identified only by your study ID number. At BBN, a computer database will be developed to analyze the data. Study participants will be identified in the database only by study ID numbers. The database will be kept in a password-protected computer. All study records at BBN, including the digital

mammographic images that will be stored on a CD-ROM, will be kept in a locked room controlled by the project's Principle Investigator.

People from the Emory University Institutional Review Board (IRB), Office for Human Research Protections (OHRP), the Food and Drug Administration (FDA), BBN Technologies and representatives of the U. S. Army Research and Materiel Command are eligible to review research records as part of their responsibility to protect human subjects.

We will not use or disclose your records in any ways other than those described in this form, and we will keep your records private to the extent allowed by law. We will do this even if outside review of your records occurs. Your name and other facts that might point to you will not appear when we present this study or publish its results.

The research and clinical mammographic images may be used by the investigators in scientific publications, posters, conferences, and for teaching purposes. These images may also be given to other researchers within Emory University and at other establishments who may need them for scientific purposes. The clinical and experimental images may be displayed at scientific presentations that are open to the public and they may also be posted electronically on the worldwide web. However, all images that may be used for the above stated purposes will be completely de-identified and it will not be possible to trace your identity from any of these images.

Protected Health Information (PHI): Protected health information (PHI) is any health information provided to persons that identifies you or information that can reasonably be used to identify you. The people who are conducting this study (the "Researchers") may need to look at your medical records that contain this PHI. In addition, government agencies that make rules and policies about how research is done, including the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA) and, have the right to review these records. Sponsors who pay for the study, the Emory University Institutional Review Board (IRB) and the U. S. Army Research and Materiel Command also have the right to review your medical records. In addition, these records may be disclosed pursuant to court order.

Under the Health Insurance Portability and Accountability Act (HIPAA), a federal law enacted to protect the privacy of your PHI, before we can use or disclose your PHI, we must provide you with information about what PHI will be used for this research study and how it will be used and disclosed. This section of this form provides you with this information regarding your PHI. Specifically, it will tell you what PHI the Researchers will look at; who will collect the PHI; who will use the PHI, with whom it will be shared and the purpose of each use or disclosure; the expiration date or event, if any, after which we won't use or disclose your PHI any more; and your rights under HIPAA to ask us not to use your PHI any more. If you decide to participate in this research, then you will be agreeing to let the

Researchers and any other persons, companies or agencies described below to use and share your PHI for the study in the ways that are set forth in this section, so please review this section very carefully.

What PHI will the Research Team Use: As part of your clinical care, the Researchers will look at information that identifies you such as your name, patient identification number, medical records number, birth date and social security number. The Researchers will also look at your medical history and at any results from laboratory tests and physical examinations that you have had performed. In addition, if you have a bad outcome or 'adverse event' then the Researchers may also need to look at your entire medical record.

Who will collect the PHI: The Researchers will collect and copy the PHI described above. If any of the PHI is to be shared with other persons, as described later on in this section, then the Researchers also will be responsible for making these disclosures.

Who will Use the PHI; With Whom will it be Shared; and For What Purpose(s) Will it be Used or Shared: In order to conduct the study, the PHI that is collected regarding you will be used by or shared with the following persons, agencies or companies for the purposes listed in the chart below.

Person/Entity	Purpose
Researchers at Emory and BBN Technologies	To conduct the study entitled, "An Evaluation of Stereoscopic Digital Mammography for Earlier Detection of Breast Cancer and Reduced Rate of Recall."
Governmental Agencies with oversight over the research being conducted, including the FDA and OHRP	To monitor safety, efficacy and compliance with applicable laws and regulations.
University personnel, committees and departments charged with oversight of research, including the IRB.	To monitor safety and compliance with applicable laws, regulations and University policies and procedures.
Representatives of the US Army Medical Research and Material Command, the study sponsors.	To provide oversight for the study and as part of their responsibility to protect human subjects.

Expiration Date or Event: The Researchers will continue to use your PHI until the study is closed and the period for which any records relating to the study must be retained has ended.

Your Right Under HIPAA to Revoke Your Authorization and Ask Us Not to Use Your PHI Any More:

Giving the Researchers your authorization to use and share your PHI is voluntary. At any time, you may choose to revoke your authorization for the Researchers to use and share your PHI. If you revoke your authorization, the Researchers may no longer be able to provide you with any research-related treatment, but your revocation will not otherwise affect your current or future health care. Further, if you revoke your authorization, there will be no penalty or loss of any benefits to which you are otherwise entitled.

If you decide that you want to revoke your authorization for us to use your PHI, you may do so by completing and signing the revocation letter that you receive with your copy of this Combined Informed Consent/HIPAA Authorization form and providing it to the researcher. If at any time you need another copy of this form, you may ask the Researchers to provide you with one. Once we receive your written revocation of your authorization to use your PHI, we will not make any other use of your PHI or share it with anyone else, except as follows: (a) we will let the study sponsor know that you have revoked your authorization; (b) we will not ask the study sponsor or any other parties to whom we said we would disclose data to return any data that we provided to it/them before you revoked your authorization; (c) and, even after we receive your revocation, we will still provide the study sponsor and any other parties to whom we stated that we would disclose data with any data that is necessary to preserve the integrity of the research study, and we will provide any governmental or University personnel, departments or committees with any data that they may need in order to comply with/or investigate adverse events or non-compliance with any applicable laws, regulations or University policies.

PHI May be Re-disclosed: If we disclose your PHI to one of the other parties described above, that party might further disclose your PHI to another party. If your PHI is further disclosed, then the information is no longer covered by HIPAA.

Signature and Date: The Researchers will ask you to sign and date this form. A copy of your signed and dated consent/authorization will be placed in your medical record(s).

We will give you a copy of this signed consent form to keep.

If you're willing to volunteer for this research, please sign the next page.

Subject's Printed Name

Subject's Phone Number

Subject's Signature

Date

Time

Person Obtaining Consent

Date

Time

03-05-02

Revised 04-19-02

Revised 12-27-02

Revised 01-29-03

Revised 03-05-03

Revised 04-02-03

Revised 05-02-03

Revised 07-21-03

Revised 03-16-04

Revised 06-23-04

Revised 12-16-04

Revised 04-26-2005

REVISED 07-21-2007

SDM DATA FORM A1 - STANDARD READING

Appendix C

PATIENT STUDY NUMBER: _____

DATE OF EXAM: _____

DATE OF READING: _____

READER'S INITIALS: _____

1. Prior films present with interpretation? ☐ Yes ☐ No

2. Breast composition: ☐ Fatty ☐ Scattered densities ☐ Heterogeneously dense ☐ Extremely dense

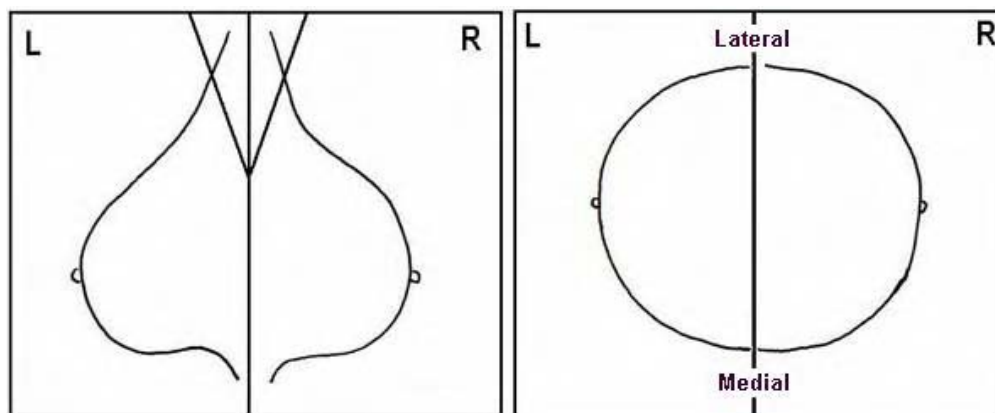
3. Number of findings in each breast that require work-up: LEFT _____ RIGHT _____
(If NONE, skip to 6)

4. On the picture below mark all of those findings.

Use the following codes: **M**-Mass, **M/C** – Mass w/ calcifications, **F**- Focal asymmetry,

A- Architectural distortion, **C** – Clustered Calcifications.

(Numbers starting with 1 can be appended to the code for more than one finding of the same type).



5. For each finding, rate the following characteristics and indicate recommended work-up action(s):

Finding Code	Confidence of True Finding (0 to 100 scale)	Conspicuity (1=Barely visible to 10=Highly visible)	Likelihood of Malignancy (0 to 100 scale)	BIRADS Category for finding	Indicate recommended work-up action(s)						
					Spot	Mag	Roll	90	Exag.	US	Other (Specify)

6. Indicate all benign findings (Select all that apply):

Circumscribed mass(es)	Benign calcifications	Unchanged low suspicion calcifications	Post radiation therapy/lumpectomy	IM nodes
<u>Right</u> <u>Left</u> <input type="checkbox"/> UOQ <input type="checkbox"/> <input type="checkbox"/> UIQ <input type="checkbox"/> <input type="checkbox"/> LIQ <input type="checkbox"/> <input type="checkbox"/> LOQ <input type="checkbox"/>	<u>Right</u> <u>Left</u> <input type="checkbox"/> UOQ <input type="checkbox"/> <input type="checkbox"/> UIQ <input type="checkbox"/> <input type="checkbox"/> LIQ <input type="checkbox"/> <input type="checkbox"/> LOQ <input type="checkbox"/>	<u>Right</u> <u>Left</u> <input type="checkbox"/> UOQ <input type="checkbox"/> <input type="checkbox"/> UIQ <input type="checkbox"/> <input type="checkbox"/> LIQ <input type="checkbox"/> <input type="checkbox"/> LOQ <input type="checkbox"/>	<u>Right</u> <u>Left</u> <input type="checkbox"/> UOQ <input type="checkbox"/> <input type="checkbox"/> UIQ <input type="checkbox"/> <input type="checkbox"/> LIQ <input type="checkbox"/> <input type="checkbox"/> LOQ <input type="checkbox"/>	<u>Right</u> <u>Left</u> <input type="checkbox"/> UOQ <input type="checkbox"/> <input type="checkbox"/> UIQ <input type="checkbox"/> <input type="checkbox"/> LIQ <input type="checkbox"/> <input type="checkbox"/> LOQ <input type="checkbox"/>
Unchanged post percutan. needle biopsy <u>Right</u> <u>Left</u> <input type="checkbox"/> UOQ <input type="checkbox"/> <input type="checkbox"/> UIQ <input type="checkbox"/> <input type="checkbox"/> LIQ <input type="checkbox"/> <input type="checkbox"/> LOQ <input type="checkbox"/>	Post benign surgical excision <u>Right</u> <u>Left</u> <input type="checkbox"/> UOQ <input type="checkbox"/> <input type="checkbox"/> UIQ <input type="checkbox"/> <input type="checkbox"/> LIQ <input type="checkbox"/> <input type="checkbox"/> LOQ <input type="checkbox"/>	Unchanged focal/general asymmetry <u>Right</u> <u>Left</u> <input type="checkbox"/> UOQ <input type="checkbox"/> <input type="checkbox"/> UIQ <input type="checkbox"/> <input type="checkbox"/> LIQ <input type="checkbox"/> <input type="checkbox"/> LOQ <input type="checkbox"/>	Other: <u>Right</u> <u>Left</u> <input type="checkbox"/> UOQ <input type="checkbox"/> <input type="checkbox"/> UIQ <input type="checkbox"/> <input type="checkbox"/> LIQ <input type="checkbox"/> <input type="checkbox"/> LOQ <input type="checkbox"/>	

7. BIRADS Category for patient: _____

Comments:

SDM DATA FORM A2 - STEREO READING

Appendix D

PATIENT STUDY NUMBER: _____

DATE OF EXAM: _____

DATE OF READING: _____

READER'S INITIALS: _____

1. Prior films present with interpretation? ☐ Yes ☐ No

2. Breast composition: ☐ Fatty ☐ Scattered densities ☐ Heterogeneously dense ☐ Extremely dense

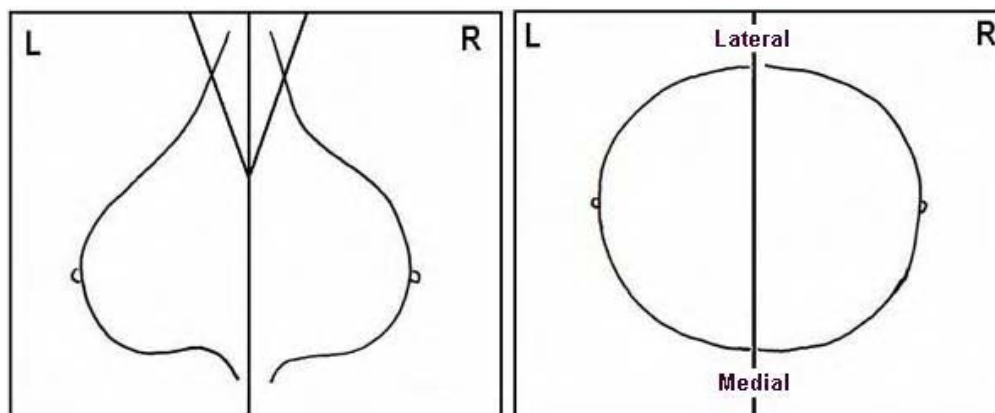
3. Number of findings in each breast that require work-up: LEFT _____ RIGHT _____
(If NONE, skip to 6)

4. On the picture below mark all of those findings.

Use the following codes: **M**-Mass, **M/C** – Mass w/ calcifications, **F**- Focal asymmetry,

A- Architectural distortion, **C** – Clustered Calcifications.

(Numbers starting with 1 can be appended to the code for more than one finding of the same type).



5. For each finding, rate the following characteristics and indicate recommended work-up action(s):

Finding Code	Confidence of True Finding (0 to 100 scale)	Conspicuity (1=Barely visible to 10=Highly visible)	Likelihood of Malignancy (0 to 100 scale)	BIRADS Category for finding	Indicate recommended work-up action(s)						
					Spot	Mag	Roll	90	Exag.	US	Other (Specify)

6. Indicate all benign findings (Select all that apply):

Circumscribed mass(es)	Benign calcifications	Unchanged low suspicion calcifications	Post radiation therapy/lumpectomy	IM nodes
<u>Right</u> <u>Left</u> <input type="checkbox"/> UOQ <input type="checkbox"/> <input type="checkbox"/> UIQ <input type="checkbox"/> <input type="checkbox"/> LIQ <input type="checkbox"/> <input type="checkbox"/> LOQ <input type="checkbox"/>	<u>Right</u> <u>Left</u> <input type="checkbox"/> UOQ <input type="checkbox"/> <input type="checkbox"/> UIQ <input type="checkbox"/> <input type="checkbox"/> LIQ <input type="checkbox"/> <input type="checkbox"/> LOQ <input type="checkbox"/>	<u>Right</u> <u>Left</u> <input type="checkbox"/> UOQ <input type="checkbox"/> <input type="checkbox"/> UIQ <input type="checkbox"/> <input type="checkbox"/> LIQ <input type="checkbox"/> <input type="checkbox"/> LOQ <input type="checkbox"/>	<u>Right</u> <u>Left</u> <input type="checkbox"/> UOQ <input type="checkbox"/> <input type="checkbox"/> UIQ <input type="checkbox"/> <input type="checkbox"/> LIQ <input type="checkbox"/> <input type="checkbox"/> LOQ <input type="checkbox"/>	<u>Right</u> <u>Left</u> <input type="checkbox"/> UOQ <input type="checkbox"/> <input type="checkbox"/> UIQ <input type="checkbox"/> <input type="checkbox"/> LIQ <input type="checkbox"/> <input type="checkbox"/> LOQ <input type="checkbox"/>
Unchanged post percutan. needle biopsy <u>Right</u> <u>Left</u> <input type="checkbox"/> UOQ <input type="checkbox"/> <input type="checkbox"/> UIQ <input type="checkbox"/> <input type="checkbox"/> LIQ <input type="checkbox"/> <input type="checkbox"/> LOQ <input type="checkbox"/>	Post benign surgical excision <u>Right</u> <u>Left</u> <input type="checkbox"/> UOQ <input type="checkbox"/> <input type="checkbox"/> UIQ <input type="checkbox"/> <input type="checkbox"/> LIQ <input type="checkbox"/> <input type="checkbox"/> LOQ <input type="checkbox"/>	Unchanged focal/general asymmetry <u>Right</u> <u>Left</u> <input type="checkbox"/> UOQ <input type="checkbox"/> <input type="checkbox"/> UIQ <input type="checkbox"/> <input type="checkbox"/> LIQ <input type="checkbox"/> <input type="checkbox"/> LOQ <input type="checkbox"/>	Other: <u>Right</u> <u>Left</u> <input type="checkbox"/> UOQ <input type="checkbox"/> <input type="checkbox"/> UIQ <input type="checkbox"/> <input type="checkbox"/> LIQ <input type="checkbox"/> <input type="checkbox"/> LOQ <input type="checkbox"/>	

7. BIRADS Category for patient: _____

Comments:

SDM DATA FORM B – CONSENSUS /RESOLUTION OF FINDINGS

PATIENT STUDY NUMBER: _____

DATE OF EXAM: _____

DATE OF CONSENSUS MEETING: _____

READER INITIALS: STANDARD _____ STEREO _____

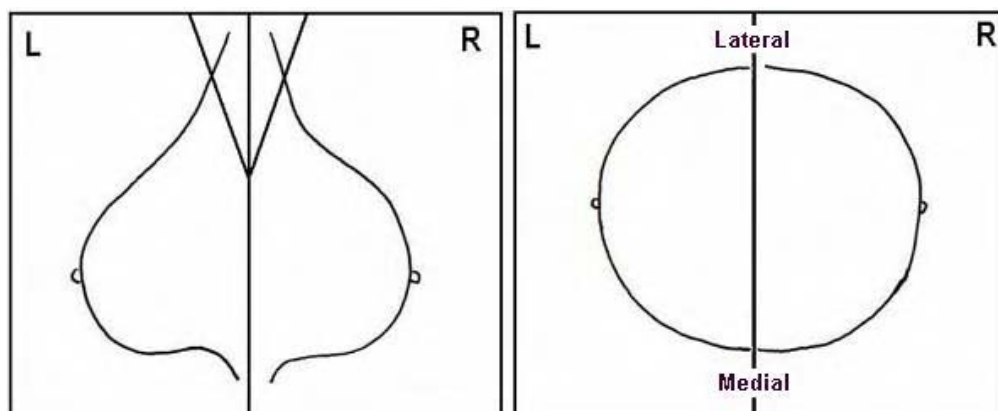
1. For each finding (from either the standard or stereo readings), indicate the correspondence between the findings in the standard and stereo readings.

Use the following codes: **M**-Mass, **M/C** – Mass w/ calcifications, **F** – Focal asymmetry, **A** – Architectural distortion, **C** – Clustered Calcifications, **ND** – Not detected in that reading.

(Numbers starting with 1 can be appended to the code for more than one finding of the same type).

Finding #	Finding Code		Basis of Discrepancy (if any)
	Standard	Stereo	
1			
2			
3			
4			

2. On the picture below mark each of the findings, using the above sequential finding numbers (1,2,3,4).



3. Recommended work-up actions:

Finding #	Indicate work-up action(s)						
	Spot	Mag	Roll	90	Exaggerated	Ultra-sound	Other (specify)
1							
2							
3							
4							

4. BIRADS Category for patient: _____ Comments:

SDM DATA FORM C – WORK-UP RESULTS

PATIENT STUDY NUMBER: _____

DATE OF WORK-UP EXAM: _____

DATE OF READING: _____

READER'S INITIALS: _____

Use the following codes: **M** – Mass, **M/C** – Mass w/ calcifications, **F** – Focal asymmetry,
A – Architectural distortion, **C** – Calcifications, **Ø** – No finding.
(Numbers starting with 1 can be appended to the code for more than one finding of the same type).

For Ultrasound, use the following codes: **SM** – Solid mass, **FM** – Fluid-filled mass

1. Work-up performed:

Finding #	Finding Code		Indicate work-up finding results (using above codes)						
	Std.	Stereo	Spot	Mag	Roll	90	Exag-gerated	Ultra-sound	Other (specify)
1									
2									
3									
4									

2. For each finding, determine a final, combined finding code, rate the likelihood of malignancy, specify whether biopsy is required, and the BIRADS category:

Finding #	Final Work-up Finding Code	Likelihood of Malignancy (0 to 100 scale)	Biopsy Required? (Y or N)	BIRADS Category for finding
1				
2				
3				
4				

3. BIRADS Category for patient: _____

Comments:

SDM DATA FORM D – BIOPSY

PATIENT STUDY NUMBER: _____

DATE OF BIOPSY: _____

PATHOLOGIST'S INITIALS: _____

Use the following codes: **M** – Mass, **M/C** – Mass w/ calcifications, **F** – Focal asymmetry,
A – Architectural distortion, **C** – Calcifications.

(Numbers starting with 1 can be appended to the code for more than one finding of the same type).

Biopsy results:

Finding #	Final Work-up Finding Code	Type of Biopsy: Excision (E), Percutaneous (P)	Malignant (M) or Benign (B)?	Pathology Code(s) <i>(Use pathology codes listed below)</i>
1				
2				
3				
4				

PATHOLOGY CODES**Benign**

1.	Atypical Columnar Hyperplasia	ACH
2.	Atypical Ductal Hyperplasia	ADH
3.	Atypical Lobular Hyperplasia	ALH
4.	Benign Cystosarcoma Phylloides	BPT
5.	Columnar Hyperplasia	CH
6.	Cysts	BC
7.	Diabetic mastopathy	DF
8.	Ductal Ectasia	DE
9.	Ductal Hyperplasia (usual type)	DH
10.	Fat necrosis	FN
11.	Fibroadenoma	FA
12.	Fibrocystic Disease	FCD
13.	Granular Cell Tumor	GC
14.	Hamartoma	HB
15.	Lipoma	LB
16.	Lobular Hyperplasia	LH
17.	Papilloma	PA
18.	Pseudoagiomatous stromal hyperplasia	PSH
19.	Radial Sclerosing Scar	RS
20.	Sclerosing Adenosis	SA
21.	Other Benign	OB

Malignant

1.	Ductal Carcinoma In Situ	DS
2.	Invasive Ductal Carcinoma	IDC
3.	Invasive Lobular Carcinoma	ILC
4.	Invasive Papillary Carcinoma	IP
5.	Lymphoma	LA
6.	Medullary Carcinoma	MC
7.	Mucinous Carcinoma	CC
8.	Tubular Carcinoma	TC
9.	Other Malignant	OM

Stereoscopic digital mammography: perceptual and display factors leading to improved early detection of breast cancer

David J. Getty

BBN Technologies, 10 Moulton Street, Cambridge, Massachusetts, 02138, U.S.A.
getty@bbn.com

Abstract. Stereoscopic digital mammography holds the promise of improving the early detection and diagnosis of breast cancer compared to standard planar views. A stereo mammogram provides the radiologist with an in depth view of the breast, in which a subtle lesion is directly seen volumetrically. The increased detection sensitivity from stereo seems to arise from the separation of overlying and underlying normal tissue from the lesion, and also from capabilities provided to the reader to manipulate characteristics of the displayed stereo image. In a recently completed project, stereo mammography was shown to significantly improve diagnostic accuracy and led to detection of a significant number of new lesions in the stereo mammograms *that were not detected in the films*.

1. Stereoscopic versus Planar Digital Mammography

Standard planar mammography is widely regarded as one of the most difficult radiographic exams to interpret. It is often difficult to detect a very subtle lesion because of superimposed overlying and underlying normal tissue that masks its presence. To confirm a lesion as real, a radiologist has to find it in each of two orthogonal views. And constructing a mental image of the three-dimensional structure of a lesion from two orthogonal projections is a difficult task, at best.

Stereoscopic digital mammography holds the promise of significantly reducing these problems. In a stereo mammogram, a radiologist is able to directly view tissue and the internal structure within the breast in depth. With stereo, detection of subtle lesions is improved because overlying and underlying normal tissue, superimposed on the lesion in 2D projections, is separated away from the lesion in depth. With stereo, false alarms are reduced because normal tissue lying at different depths, aligned by chance in a 2D projection, does not superimpose to resemble a focal abnormality.

With stereo, classification accuracy is improved because the stereo mammogram enables a direct perception of a lesion's volumetric shape. Also, by separating the lesion from superimposed tissue, the stereo mammogram can present the critical diagnostic features in a clearer and sharper form. For a cluster of microcalcifications, the volumetric distribution of the elements can be directly appreciated. This is novel information since finding a one-to-one correspondence of many elements in orthogonal 2D projections is essentially impossible.

2. Stereoscopic Image Acquisition and Display

We have been acquiring stereoscopic digital mammograms, illustrated in Fig. 1, on a GE Senographe 2000D with the x-ray source rotated by 6 degrees between exposures while the position of the breast and the digital detector remains fixed, as shown in Fig. 2. The stereo pair of mammographic images is viewed by the radiologist on a stereo display workstation, shown in Fig. 3, while wearing special stereo-viewing glasses made by StereoGraphics,. The two images are presented alternately in rapid succession (at a 120 Hz. refresh rate) on a high-resolution (2300 x 1900 pixel) MegaScan monochrome monitor. The stereo-viewing glasses contain LCD lenses that function as optical shutters. They are synchronized to the display and alternately block each eye's view of the display—effectively routing each image to the appropriate eye. The radiologist's visual system fuses the two images into a single in-depth perceived image of the internal structure of the breast.

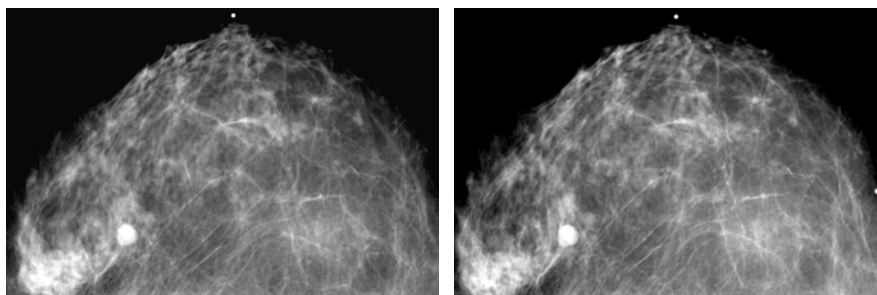


Fig. 1. Stereoscopic pair of digital mammograms, with a benign mass at 8 o'clock. It is possible to fuse these two images into a single image seen in depth by crossing one's eyes.

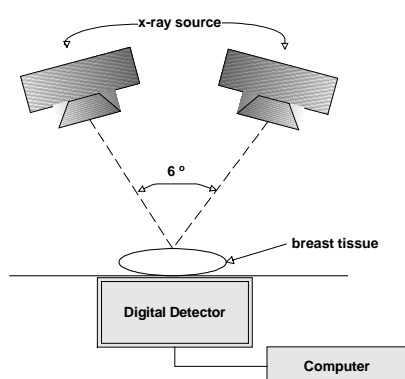


Fig. 2. Stereo mammogram acquisition.



Fig. 3. Stereo display workstation.

Because of their separation, our two eyes have slightly different views of the world. There is sufficient information in these two differing views for the visual system to determine the relative depth of different objects in the visual scene. The perceptual result is a single fused image with objects seen as distributed in depth.

This visual process is called “stereopsis.” The basis of stereopsis is the angular horizontal disparity between corresponding points of an object in the two retinal images. When you fixate an object, your eyes rotate, or “converge,” to bring the point of fixation onto the fovea of each retina. There is zero retinal disparity in the depth “plane” defined by the point of fixation. A point on an object that lies farther away from you than the fixation point creates images on the two retinas that have “positive” retinal disparity, determined by the angular difference of the corresponding points from the fovea on the two retinas. Similarly, a point that lies closer to you than the fixation point creates retinal images that have “negative” retinal disparity. The magnitude and sign of the retinal disparity are sufficient to determine an object’s depth relative to the point of fixation.

In a stereo display, retinal disparity is created by horizontal parallax—the separation of corresponding points in the left- and right-eye images on the display screen. There are three types of parallax, illustrated below in Fig. 4. If a point belonging to an object is displayed at exactly the same position in the left- and right-eye images, then it is said to have “zero parallax.” The perceptual effect is that the object is seen to lie at the surface of the display screen.

In the other two cases, a point belonging to an object is displayed at different locations in the left- and right-eye image. If the right-eye point is displaced to the right of the left-eye point, then the object will be perceived to lie behind the screen surface. The larger the separation, the farther the object will be from the screen surface. This case is called “uncrossed” or “positive” parallax.

In the third case, if the right-eye point is displaced to the left of the left-eye point, then the object will be perceived to lie in front of the display surface. Again, the larger the separation, the farther the object will be from the screen surface.

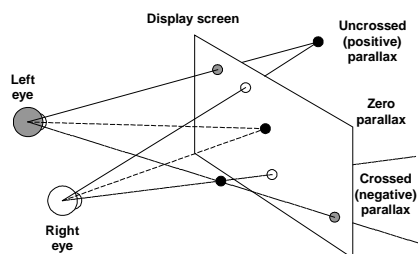


Fig. 4. Three cases of horizontal parallax. Images for the left eye (filled dots) and right eye (open dots) are shown superimposed on the display screen.

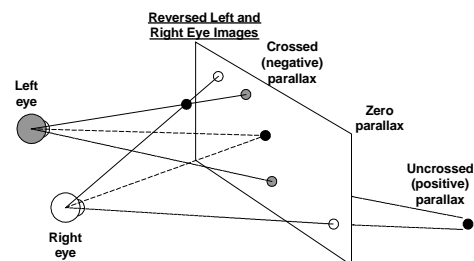


Fig. 5. Inversion of depth resulting from swapping left- and right-eye images. Compare to Fig. 4.

While the stereo point-of-view of the displayed breast tissue is determined by the point-of-view at image acquisition, there are two other aspects of the viewed volume that the user can manipulate. First, one can invert depth by swapping the two images—presenting the left-eye image to the right eye and the right-eye image to the left eye. Consider the two points corresponding to uncrossed parallax in Fig. 4. When we swap the images, as shown in Fig. 5, the filled dot becomes the open dot and vice versa. So now we have crossed parallax and the object will be seen not

behind the screen, but in front of it. Similarly, dots originally displaying crossed parallax will now have uncrossed parallax. Thus, objects originally seen in front of the screen will now be seen behind it, and vice versa. Dots with zero parallax will still have zero parallax, and remain seen at the screen surface. Thus, the effect of swapping images is to invert depth—much like reaching into a glove in a pressurized bio-isolation chamber and pulling it inside out. If, in addition to swapping the two images, one also spins each image 180 degrees about a vertical axis, then the inverted depth image is seen as if one had walked around the object to view it from the backside.

Inverting depth can be important in stereo viewing, especially of stereo mammograms. The visual system is set up to attend much more strongly to objects seen in the foreground, as opposed to the background. By allowing a radiologist to invert depth, tissue originally at the back of the displayed breast volume can be moved to the front of the volume, making it easier to perceive structure there.

A second aspect of the viewed volume that can be manipulated is the location of the displayed volume in depth with respect to the screen surface. If one shifts the right-eye image slightly to the left while holding the left-eye image fixed, as shown in Fig. 6, then the horizontal parallax of all points will be changed in the direction of uncrossed parallax. Points originally with uncrossed parallax will have larger uncrossed parallax, and points with crossed parallax will have decreased crossed parallax. The perceived effect is to shift the entire viewed volume forward in depth, with the amount of shift in depth proportional to the amount of left lateral shift of the right-eye image. Shifting the right-eye image in the other direction, to the right, will shift the viewed volume away from the viewer relative to the screen surface. It is only the amount of relative shift of the two images that matters, so one could just as well make shifts to the left-eye image, or to both.

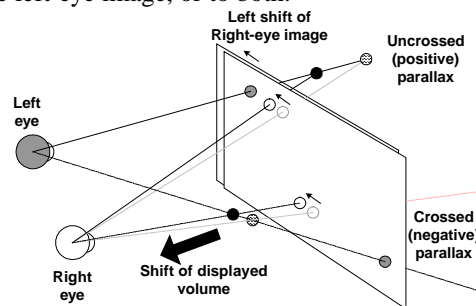


Fig. 6. Shift of the displayed volume towards the viewer with a left shift of the right-eye image.

Control of volume location is useful in that many people initially find it difficult to perceive a displayed volume that begins at the screen surface and comes towards one in space. Usually, they are more comfortable with a displayed volume that starts at the screen surface and goes back into the monitor. It's always possible to achieve this condition by using relative shifts of the two images. On the other hand, with increasing experience, people often come to prefer a displayed volume that comes out into space. As an interesting note, when the stereo image is occupying accessible physical space in front of the screen, one can actually use a pencil to point to an object of interest within the volume that other viewers can see.

3. Evaluation of Stereoscopic Digital Mammography

A project has recently been completed to evaluate the improvement in diagnosis of breast cancer achieved by stereo mammography. Over several years we acquired both standard film and stereo digital mammographic images on a number of women scheduled for biopsy of a suspicious focal breast lesion. We conducted a reading study to determine the diagnostic accuracy achieved by standard film alone compared to standard film read together with the stereo mammogram. A second goal, added as the project progressed, was to obtain preliminary data on the capability of stereo mammography to detect subtle lesions that are not visible in the corresponding film studies.

The reading study was conducted with 5 experienced mammographers individually reading 129 path-proven cases with 137 malignant and benign lesions. The reading of each case was conducted in two successive stages. The reader first examined the full set of film mammograms from the diagnostic study that led to biopsy, rating the probability that the lesion was malignant on a scale of 0 to 100. The reader was then shown the stereo view of the lesion and asked to again rate the probability of malignancy. The stereo image was always a CC view acquired just prior to biopsy. For each case, the reader was also asked to report on any additional lesions seen in either the films or the stereo mammogram, in addition to the known, biopsied lesion.

We conducted an ROC-based analysis of the accuracy of the readers' predictions of malignancy for the two viewing conditions. Diagnostic accuracy, measured by Az (the area under the ROC curve), was .83 when the readers viewed the film study alone, rising to .86 when readers also viewed the stereo mammogram. This is a statistically significant improvement.

Perhaps a more important finding was that readers detected a very significant number of likely new lesions in the stereo mammogram—ones that were not detected in the films. In all, 39 new lesions were reported in the 129 cases, corresponding to 30% of the cases. Of these 39 lesions, 30 were reported as masses, 6 as new calcification clusters, and 3 as architectural distortions. We are still awaiting confirmation of some of these lesions from later mammograms. However, we do have truth now on one subset: masses detected only in the stereo mammogram in association with prior film-detected calcifications. Of 12 such cases, the path report for 11 of the 12 cases reported that the calcifications were located *within a mass*.

4. Conclusions

Stereo mammography, as an adjunct to film, significantly improves classification accuracy of detected lesions. Perhaps of more importance is the finding that stereo mammography appears to be more sensitive than standard film mammography in detecting subtle masses and architectural distortion, enabling mammographers to detect possible lesions that are not visible on standard films. The increased detection sensitivity from stereo seems to arise from the separation of overlying and underlying normal tissue from the lesion, and also from the reader's ability to manipulate characteristics of the displayed image, including inversion of depth and grayscale windowing. Significantly, stereo mammography would be relatively easy to implement on the new digital mammography systems now being developed.

David J. Getty, PhD

Stereoscopic and Biplane Imaging¹

A difficulty with standard projection radiography is that subtle lesions can be obscured by superimposed normal tissue and anatomic structure. Stereoscopic imaging can often resolve this problem by visually separating the superimposed tissue and structure from the lesion in depth, allowing a radiologist to detect the lesion. A second difficulty with projection radiography is that chance superimposition of normal tissue or structure can mimic the appearance of an abnormality, leading to a false-positive detection. Stereoscopic imaging can help to reduce such false-positive findings because the superimposed tissue, now seen as distributed in depth, is much less likely to be perceived as a real lesion. Stereoscopic viewing also has advantages with regard to detected lesions. The location of a lesion in relation to the surrounding tissue and structure can be viewed directly, rather than inferred mentally from multiple planar views. The volumetric shape of a mass or the geometric structure of a cluster of calcifications can also be seen directly.

Many of these advantages of stereoscopic viewing were appreciated early in the development of radiography. Only a few months after the discovery and public disclosure of x rays by Röntgen in 1895, E. Thomson described the acquisition and viewing of stereoscopic x-ray images (1). The medical value of stereoscopic x-ray imaging for localization of tissues and seeing structures in depth was soon appreciated by Sir James Mackenzie Davidson, a prominent British physician who in 1898 published an article on the subject in the *British Medical Journal* (2) and in 1916 published a book containing many illustrative stereoscopic images to demonstrate the utility of stereoscopic x-ray imaging (3).

That so little time passed between the discovery of x rays and the creation of the first stereoscopic x-ray images is not so surprising, given that stereoscopic photography was a popular pastime at the beginning of the past century. It was commonplace for a family to own a parlor version of the Holmes stereoscope (4), an adaptation of an earlier stereoscope developed by Brewster in 1849 (5). Printed stereo cards provided dramatic in-depth views of places and people from around the world.

During the early part of the 20th century, devices were developed to aid the radiologist in viewing a stereo pair of x-ray images. In one type of aid, the x-ray films were mounted side by side on a light box, and a handheld viewing device, which incorporated mirrors (and sometimes lenses) in a metal frame, was held up in front of the x-ray images so that each image was seen by only one eye (Fig 1). This process was awkward, and because it was difficult to align the films precisely, radiologists often experienced some discomfort and eyestrain in using the device. Nevertheless, the added



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value of seeing the imaged tissue and anatomic structures in depth was such that stereo x-ray imaging remained a commonly used technique in radiology departments until the advent of serial section-based x-ray techniques, such as computed tomography (CT) and magnetic resonance (MR) imaging. Over the years, stereoscopic imaging has been applied, to advantage, to many different parts of the human body, including the brain (6), the cranium and face (7,8), the middle ear (9), the larynx (10), the hand and wrist (11), the spine (12–14), the rib cage (15), the pelvis (16), the breast (17,18), and the vascular system (19–21).

In recent years, advances in digital radiography, high-resolution digital display systems, and high-quality stereo viewing devices have made possible the development of medical stereoscopic imaging techniques that avoid the limitations of the earlier film-based methods. A stereo pair of digital x-ray images can be acquired easily and displayed to the radiologist in a way that ensures precise image registration and provides superb perception of depth in the imaged volume without visual strain. Furthermore, the digital display permits the radiologist to control and manipulate several viewed aspects of the stereo image (eg, gray-scale window level and window width, inversion of gray scale, and inversion of depth) that can greatly enhance the value of the stereo imaging.

STEREOSCOPIC VISION

Before a discussion of how stereoscopic medical images are acquired and displayed, it is helpful to review stereoscopic vision briefly. Our visual system provides us with a strong sense of where objects that we see before us are located in depth, relative to one another. In everyday life, the sense of depth receives contributions from many visual cues. Most of these cues are monocular, requiring only one eye to deliver the information. Examples of such cues are the relative retinal size of familiar objects, interposition and occlusion of objects, linear perspective, aerial perspective (increasing blueness and blurring of objects with growing distance), highlights and shading from light sources, and movement parallax (22). Although these monocular cues are important to us in perceiving and navigating the world around us, they are of little or no value in discerning the relative depth of structures in medical x-ray images. However, one other potent depth cue, stereopsis (“solid seeing”), uses and requires input from both eyes to provide us with depth information. This cue has the potential to provide depth information in medical images acquired as stereo pairs.

Because our two eyes are separated by about 65 mm horizontally, each has a slightly different view of the world. You can easily demonstrate this difference to yourself by holding up one finger, looking at it first



Figure 1. Demonstration of a handheld device made many years ago for viewing a stereo pair of standard radiographs mounted side by side on a view box. The device uses two pairs of angled front-surface mirrors to redirect the image from each film to the appropriate eye while permitting the observer to look straight ahead.

with one eye (while closing the other) and then with the other. You will notice that the position of objects in the background, relative to the position of your finger, changes in the images seen by your two eyes. The basis of stereopsis is the angular horizontal disparity between corresponding points of an object in the two retinal images. When you fixate an object, your eyes rotate, or “converge,” to bring the point of fixation onto the fovea of each retina. There is zero retinal disparity in the depth “plane” defined by the point of fixation. A point on an object that lies farther away from you than the fixation point creates images on the two retinas that have “positive” retinal disparity, determined by the angular difference of the corresponding points from the fovea on the two retinas. Similarly, points on an object that lies closer to you than the fixation point create retinal images that have “negative” retinal disparity. The magnitude and sign of the retinal disparity are sufficient to determine the depth of an object relative to the point of fixation.

The visual system has evolved to take advantage of the relative depth information contained in the retinal disparity present in the retinal images of the left and right eyes. Within the visual cortex, input from the two views is fused into a single perceived view in which we see objects in depth. Julesz (23) has referred to this unitary perception as the “cyclopean eye.” He and others have developed models of how networks of binocularly driven cells in the visual cortex may cross-correlate the images from the two eyes, with different layers of topographically organized cells detecting different amounts of horizontal shift. A high correlation at a particular location in a particular layer would correspond to detection of an object in the visual field at a particular location and a particular depth.

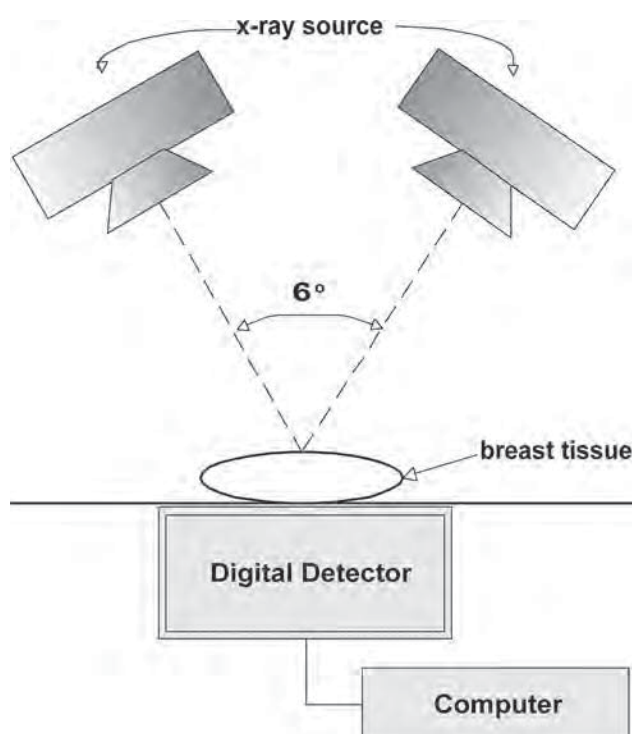


Figure 2. Acquisition of a stereo pair of digital mammograms. The x-ray source is initially rotated 3° away from the perpendicular to the digital detector surface. After one exposure, the source is then rotated by 6° (3° from the perpendicular in the other direction) before the second exposure. The detector and the tissue being imaged remain fixed in position while the source is rotated.

ACQUISITION OF STEREO IMAGE PAIRS

In a famous paper presented in 1838, Wheatstone (24) observed that one can create the perception of depth in an artificial visual scene by presenting separately to each eye a planar image corresponding to what would be seen by that eye as it observed that scene. He demonstrated his insight by creating a number of drawings of objects distributed in depth, as would be seen by the left and right eyes, and displayed them in a mirror-based stereoscope that he invented.

Photography was developing during that same era, and it was not long before Wheatstone's device was being used to view stereo pairs of photographs. To capture a stereo pair, one takes two photographs of a scene, separated by a horizontal shift of the camera of about 65 mm, corresponding to the average distance between the eyes (25). When viewed in a stereoscope that directs each image solely to the appropriate eye, the two images are fused in the mind's cyclopean eye into a single image perceived in depth, as if one were standing where the camera had been.

The same principle applies to the acquisition of stereo pairs of x-ray images. Two sequential x-ray exposures are made of the object to be imaged, with the x-ray source shifted by a small angular amount be-

tween the two exposures, as shown in Figure 2. There are, however, several important considerations in acquiring the stereo pair.

Fixed Object

It is critical that the object being imaged not move or deform in any way between the two x-ray exposures. Any such movement or deformation will result in two images that (a) create considerable visual strain and discomfort for the viewer when the visual system attempts to fuse the two into a single in-depth image or (b) simply cannot be fused. This requirement also implies that the table holding the object to be imaged must be fixed, independent of the movement of the x-ray source.

Independence of the Detector and the X-ray Source

Ideally, the x-ray detector, located beneath or behind the object to be imaged, should also remain fixed, in an unchanging relationship to the object being imaged, as the x-ray source is moved between the two exposures. In most systems, the x-ray source is mounted on a gantry such that its movement is achieved by rotation about an axis. The stereo pair of images is acquired by rotating the x-ray source by a small angle to either side of the perpendicular to the detector, as shown in Figure 2.

A problem arises, however, if the x-ray source and detector are yoked together so that both rotate together, as in some mammography systems. The resulting pair of images will suffer from keystone distortion, as shown in Figure 3. There will be noncorresponding vertical magnification in the two images that is greatest near the left and right edges. This magnification will make it difficult or impossible for a viewer to fuse the pair into a single stereo image because the visual system is intolerant of vertical disparity, which does not occur in normal vision. The situation can be remedied, however. It is possible to apply a mathematical transformation to each digital image to undo the keystone distortion—in effect, to project each image back to a fixed, correct plane. The transformation may result in a small, but probably tolerable, amount of pixel quantization error.

Angle of Separation

How much of an angular separation should one use between the two exposures in acquiring a stereo pair of x-ray images? The larger the angular separation, the greater will be the perceived depth. However, most people experience increasing visual strain when attempting to view stereo image pairs that are acquired with more than about 8° or 9° of angular separation. Thus, the angle of separation between the two images should in most cases not exceed this limit. In our own work, we have found a separation of 6° to be a good

compromise. Another issue that bears on the angle of separation and conditions for viewing the stereo image will be discussed subsequently in this chapter (see "Location of the Observer Relative to the Display Screen" section).

STEREOSCOPIC DISPLAY SYSTEMS

The goal in displaying a stereo image pair is to channel the image intended for the left eye solely to the left eye and the image intended for the right eye solely to the right eye while maintaining precise alignment of the two images. A number of methods have been developed to accomplish this goal, and they can be categorized in several ways (26). A major distinction is whether or not the observer has to wear special glasses or other headgear. Most systems, referred to simply as *stereoscopic display systems*, do require the observer to wear glasses or other gear. Other systems, referred to as *autostereoscopic display systems*, permit the observer to view the stereo image freely, without encumbrance. Both types of system are discussed in the subsequent paragraphs, with the discussion restricted to systems appropriate for the display of stereo digital radiographs.

Autostereoscopic Display Systems

Current autostereoscopic display systems that are capable of displaying medical stereo image pairs are based on "parallax barrier" techniques. The left- and right-eye images are interleaved on the display, typically a liquid crystal display (LCD), such that successive columns of pixels alternate between left- and right-eye images. In some systems, a grid plate with a series of vertical slits, at half the frequency of the pixels, is placed in front of the LCD elements. When the observer is seated directly in front of the display at a specified distance, the solid vertical strips of the grid block the right eye's view of the left-eye pixel columns and, similarly, the left eye's view of the right-eye pixel columns. In other systems, the grid is located between the illumination source and the matrix of LCD elements, creating a series of vertical light strips. Some systems have used a lenticular lens sheet placed over the LCD matrix. The sheet consists of a horizontal series of vertically oriented cylindrical lenses, each the width of two pixel columns. The lenses bend light from the left-eye columns of the LCD slightly to the left and light from the right-eye columns slightly to the right.

One major limitation of these systems is the restriction of the viewer to a particular location in front of the display. Several groups have recently worked on adding eye tracking to the display system, for example, by using two video cameras mounted on top of the display to dynamically determine the observer's current eye location and to dynamically adjust the parallax grid to channel the alternating pixel columns to the appropriate eye. If this enhancement proves effective,

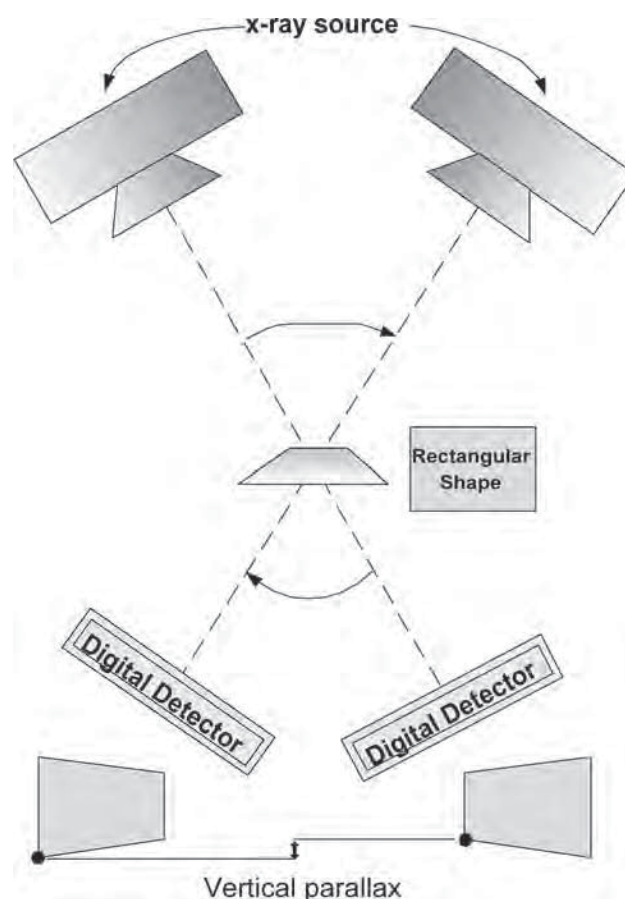


Figure 3. Linked rotation of the x-ray source and of the digital detector that results in keystone distortion in the acquired stereo pair of images. As shown, exposure of a rectangular object would result in trapezoidal images in which corresponding points in the two images would be displaced vertically, particularly near the left and right edges.

it would allow the viewer some degree of freedom to move in front of the display while maintaining a stereo image.

A second limitation of this type of display is the limited horizontal resolution. Because left- and right-eye columns of pixels alternate on the display, the horizontal pixel count is only half that of the display, with no similar reduction vertically.

Stereoscopic Display Systems

Spatially multiplexed systems.—Systems in which both left- and right-eye images are simultaneously conveyed to each eye through spatially separate channels are said to be *spatially multiplexed*. All of the mechanical stereoscopes described earlier are of this type. The simplest spatially multiplexed digital systems divide the display screen in half, with each image of the stereo pair occupying only half of the screen. A device that is held, or attaches to the front of the monitor, contains mirrors and optics that deliver each image to the appropriate eye. The obvious limitation is that horizontal pixel count is limited to half of the screen width.



Figure 4. Example of a temporally multiplexed stereoscopic display workstation. The two stereo images are presented alternately on the high-resolution monitor at a 120-Hz frame refresh rate. The small black box on top of the monitor emits an infrared synchronization signal. This signal is picked up by the special glasses worn by the observer and triggers LCD optical shutters in the two lenses to open and close in opposition, routing each image to the correct eye.

Other systems use two separate display monitors, each dedicated to just one of the images. Various devices have been devised to deliver the image of each monitor to the appropriate eye. This technique is rarely used because of the large amount of equipment involved and the difficulty of matching the two monitors and aligning the two display images precisely enough. The continuing development of miniature high-resolution displays may eventually lead to a small lightweight piece of headgear containing two small monitors that deliver a stereo image.

Temporally multiplexed systems.—By far the most common method of displaying stereo digital image pairs makes use of *temporal multiplexing*. In this case, both left- and right-eye images are displayed on a single monitor, with the two images alternately presented on successive frames. The trick, of course, is to find a way to deliver each image to the appropriate eye—and only to that eye. Current systems use special glasses equipped with LCD lenses that act as optical shutters. One such system is shown in Figure 4. Each lens can be made either clear (effectively, two layers of polarization in the same direction) or opaque (two layers of polarization at right angles). At the beginning of each successive frame, the glasses receive an infrared synchronization signal from the display controller card that enables the glasses to track when each image is being displayed on the monitor. When the left-eye image is being displayed, the left-eye lens of the glasses is clear, and the right-eye lens is opaque. On the next display frame, when the right-eye image is being displayed, the optical shutters of both lenses switch state, and so on continuously. Note that each eye is seeing only every other frame. To avoid perceived flicker of the image, the

monitor must be driven at a high refresh rate, typically on the order of 120 Hz. Thus, each eye sees an image refreshed at 60 Hz, a rate high enough to avoid flicker in most circumstances.

In a related type of system, the optical shutter is a large LCD sheet that covers the entire front surface of the monitor. The observer wears lightweight, passive polarized glasses with the axis of polarization 90° apart in the two lenses. The polarization of light passing through the LCD sheet matches that of one lens on one display frame and is rotated by 90° to match the other lens on the next display frame. The advantage of this method is the lighter weight of the glasses. A disadvantage is that the large LCD sheet is more prone to damage and, in general, must be left on the monitor all of the time.

With either method, the luminance of the image seen by the observer is reduced to about 32% of the luminance of the image present at the face of the monitor because of losses of light with passage through the LCD lens (and polarized glasses in the second technique). Thus, the brightness of the image is reduced considerably compared with a nonstereo soft-copy display.

A potential artifact with this method of display is ghosting. If the phosphor used in the monitor is relatively slow to decay after being activated on one display frame by the scanning electron beam, then an image presented, say, to the left eye may not have disappeared entirely at the start of the next frame when the right-eye lens is open. Each eye may therefore see a faint ghost of the image from the preceding frame, intended for the other eye.

This ghosting can reduce considerably the effectiveness of the stereo presentation and the amount of depth perceived in the image. Thus, there is a need to choose a phosphor for the monitor that exhibits rapid decay. One might imagine that substituting a flat-panel LCD for the cathode ray tube monitor would solve the problem. However, current LCD monitors also exhibit persistence caused by electronics and liquid crystal memory effect that can be as long as 25–50 msec. If high frame rates are used to avoid flicker, ghosting would occur because of the long pixel transition times. A second problem with current LCD monitors is that the transmitted light is polarized. This polarization will typically be in a plane that conflicts with the polarization plane of the stereo LCD glasses, and if not taken into account, it can reduce the luminance of the display.

A high-resolution, gray-scale stereo display workstation of this type has recently been developed (Fig 4). This device is capable of displaying an entire digital mammogram ($2,304 \times 1,800$ pixels) at once in stereo, at a 120-Hz refresh rate. The observer wears stereo LCD glasses that are synchronized to the display by an infrared emitter. Because of the high pixel density on the display, the observer is even able to use a magnifying

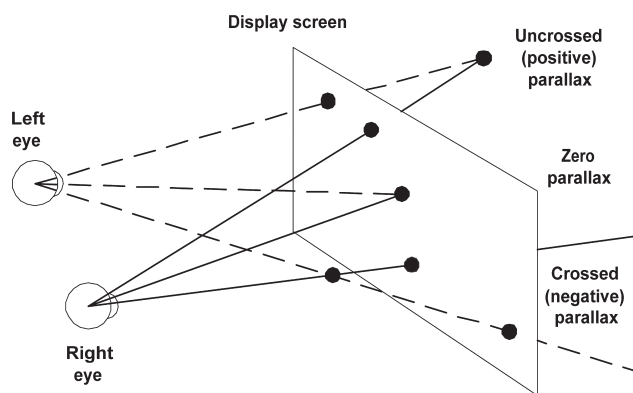


Figure 5. Illustration of uncrossed (positive), zero, and crossed (negative) parallax of pairs of corresponding points shown on a display screen. In a temporally multiplexed display, only the points intended for the right eye (solid lines) or those for the left eye (dashed lines) would be visible on the screen at one time. These points are shown together here to illustrate the perceptual effects of different types of horizontal displacement.

glass on the stereo image to observe detail, seen in depth, at greater magnification.

DISPLAY OF THE STEREO IMAGE

Horizontal Parallax

In a stereo display, the retinal disparity that leads one to perceive depth in natural vision is created by horizontal parallax—the horizontal separation of corresponding points in the left- and right-eye images on the display screen (27). There are three types of parallax, as illustrated in Figure 5. If a point belonging to an object is displayed at exactly the same position in the left- and right-eye images, then it is said to have “zero parallax.” The perceptual effect is that the object is seen to lie at the surface of the display screen.

In the other two cases, a point belonging to an object is displayed at different locations in the left- and right-eye images. If the right-eye point is displaced to the right of the left-eye point, then the object will be perceived to lie behind the screen surface. The larger the separation, the farther the object will be from the screen surface. This case is called “uncrossed” or “positive” parallax.

In the third case, if the right-eye point is displaced to the left of the left-eye point, which is called “crossed” or “negative” parallax, then the object will be perceived to lie in front of the display surface. Again, the larger the separation, the farther the object will be from the screen surface, toward the observer.

Depth Quantization

Because we are working with digital images, the amount of horizontal parallax between pairs of corresponding points in the two images is necessarily an integer multiple of the spacing between pixels. Consequently, the perceived location of points in depth will

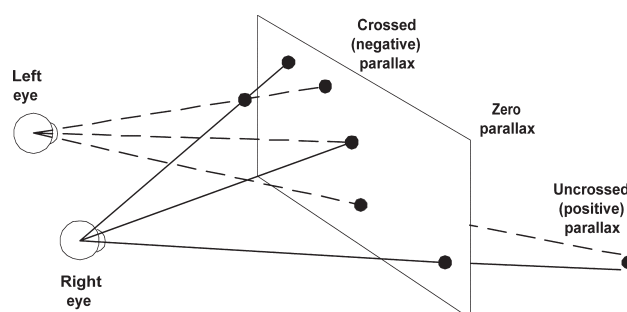


Figure 6. Inversion of perceived depth achieved by swapping the two images. Points that had been seen by the right eye in Figure 5 are now seen by the left eye (now shown with dashed lines), and points that had been seen by the left eye are now seen by the right eye (now shown with solid lines). By comparing this figure with Figure 5, one can see that depth has been inverted: points that showed uncrossed parallax in Figure 5 now exhibit crossed parallax, and those that showed crossed parallax now exhibit uncrossed parallax. Points with zero parallax remain unchanged.

also occur in quantized depth planes. The actual functional relationship between pixel spacing and depth plane spacing also depends on the distance of the observer from the display screen, as will be discussed subsequently (see “Location of the Observer Relative to the Display Screen” section).

Manipulations of the Stereo Image

Inversion of depth.—Although the stereo point of view of the imaged object is predetermined by the point of view at the time of image acquisition, the observer can manipulate two other aspects of the viewed volume (27). First, one can invert depth by swapping the two images—presenting the left-eye image to the right eye and the right-eye image to the left eye. Consider the two points corresponding to uncrossed parallax in Figure 5. When we swap the images, as shown in Figure 6, the dot previously seen by the left eye is now seen by the right eye, and vice versa. So now we have crossed parallax, and the object will be seen not behind the screen but in front of it. Similarly, dots originally displaying crossed parallax will now have uncrossed parallax. Thus, objects originally seen in front of the screen will now be seen behind it, and vice versa. Dots with zero parallax will still have zero parallax and continue to be seen at the screen surface. Thus, the effect of swapping images is to invert depth—much like reaching into a glove and pulling it inside out. If, in addition to swapping the two images, one also spins each image 180° about a vertical axis, then the inverted depth image is seen as if one had walked around the object to view it from the back.

Inverting depth can be important in stereo viewing, especially of mammograms. It is easier to attend to objects seen in the foreground than those seen in the background, especially when there is a clutter of objects in the foreground. When a radiologist is allowed

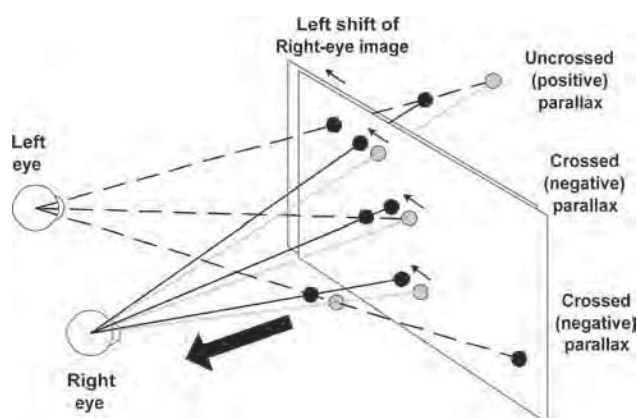


Figure 7. Shifting of the displayed volume either toward or away from the observer through horizontal shifts of one or both images relative to the other. This figure illustrates a leftward shift of the right-eye image relative to the left-eye image, which causes the entire displayed volume to shift toward the observer. A rightward relative shift of the right-eye image relative to the left-eye image would cause the displayed volume to move away from the observer.

to invert depth, tissue originally at the back of the displayed volume can be moved to the front of the volume, making the tissue easier to perceive and inspect.

Shifting location of the viewed volume.—A second aspect of the viewed volume that can be manipulated is the location of the displayed volume in depth with respect to the screen surface. If one shifts the right-eye image slightly to the left while holding the left-eye image fixed, as shown in Figure 7, then the horizontal parallax of all points will be changed in the direction of uncrossed parallax. Points originally with uncrossed parallax will have larger uncrossed parallax, and points with crossed parallax will have decreased crossed parallax. The perceived effect is to shift the entire viewed volume forward in depth, toward the observer, with the amount of shift in depth proportional to the amount of left lateral shift of the right-eye image. Shifting the right-eye image in the other direction, to the right, will shift the viewed volume away from the viewer relative to the screen surface. It is only the amount of relative shift of the two images that matters, so one could just as well make shifts to the left-eye image or to both images. In fact, splitting a desired amount of shift between the two images will minimize the amount of stereo image lost at the left and right edges of the display.

Control of location of the viewed volume is useful in that many people initially find it difficult to perceive a displayed volume that begins at the screen surface and comes toward them in space. They are usually more comfortable with a displayed volume that starts at the screen surface and goes back into the monitor. It is always possible to achieve this condition by using relative shifts of the two images. On the other hand, with increasing experience, people often come to prefer a

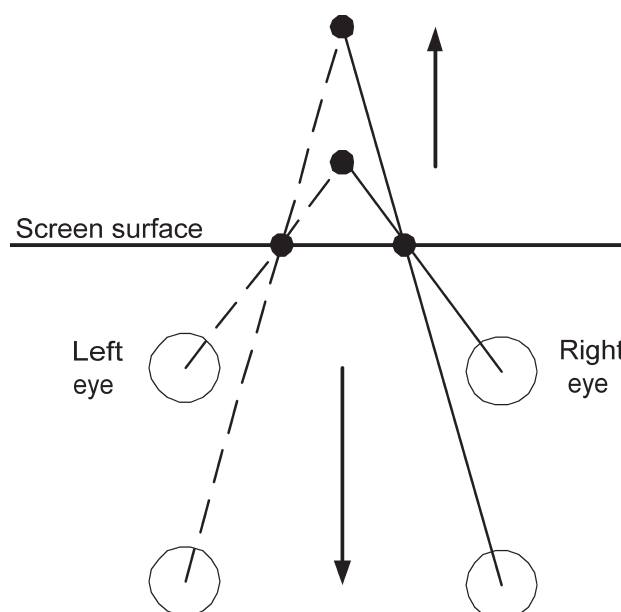


Figure 8. Relationship between distance of the observer from the display screen surface and perceived depth of a point displayed with fixed horizontal parallax between the left- and right-eye images. Increasing observer distance from the display screen results in greater perceived depth in the stereo image.

displayed volume that comes out into space. As an interesting note, when the stereo image is occupying accessible physical space in front of the screen, one can actually use a finger or pencil to point out to other observers an object of interest within the volume.

PERCEPTUAL CHARACTERISTICS OF THE STEREO IMAGE

Location of the Observer Relative to the Display Screen

Does it matter how close or far away the observer is from the display screen? In part, the answer is “yes.” In Figure 8, two corresponding points, one intended for the left eye and the other for the right eye, are shown with uncrossed parallax, resulting in perception of a point located behind the display screen. If the observer moves back from the closer viewing position to the more distant one, the location of the perceived point moves further back in depth. The two distances are directly proportional to one another. Thus, as the observer moves away from the display screen, the amount of perceived depth in the displayed stereo image will increase.

Is there a “correct” distance, then, for the observer to be from the screen? If the observer wants the amount of perceived depth to be the same as the actual depth that was present in the imaged object, then the answer is again “yes.” As shown in Figure 9, the observer wants to be at a distance from the screen such that the angle, α , formed between the observer’s two eyes and

a central point on the screen, is equal to the separation angle used in acquiring the stereo image pair. For an acquisition separation angle of 6° , the appropriate viewing distance is about 62 cm (about 24 inches). If the observer is farther away than this distance, perceived depth will be greater than the actual depth of the object; if the observer is closer, then perceived depth will be less than actual depth. The relationship is given by the following formula: correct viewing distance = $3.25 \text{ cm} / \tan(\text{acquisition angle}/2)$, where 3.25 cm represents half of the average interocular spacing of 6.5 cm. The smaller the separation angle at acquisition, the larger the correct viewing distance. In practical terms, one's perception of this change in depth with viewing distance is small for the range of distances that a radiologist finds comfortable and useful and is therefore not of much consequence.

Because corresponding points in the two images of a stereo pair bear a fixed relationship to one another—determined at the time of image acquisition—sideways movement of the observer causes the viewed stereo image to appear to rotate, so as always to present exactly the same point of view to the observer. Because the two images are fixed, the observer cannot alter his or her point of view of the object by moving from side to side. Also, the observer should not tilt his or her head while viewing the stereo image. Head tilt will cause corresponding points in the two images to be displaced from one another vertically on the two retinas, making it increasingly difficult to fuse the two images with increasing tilt.

Depth Acuity

Our ability to discriminate the relative depth of objects in normal vision—to say which is nearer, for example—is remarkably good. Depth acuity is usually measured in terms of the difference in angle two objects at different depths create at the two eyes. Studies have shown that when the objects are vertical line segments, we can detect a difference in depth corresponding to as little as 2–6 seconds of arc (28).

Some studies of depth acuity have been conducted for accuracy of placement of a cross-hair cursor in depth in digital stereo mammograms. Goodsitt et al (29,30) acquired a stereo x-ray image of a phantom containing low-density fibrils with both vertical and horizontal orientations, at depths ranging from 1 to 11 mm. The observer's task was to move a cursor to the depth of each fibril while viewing the stereo image. They found that observers were able to place the cursor accurately for vertical fibrils, with standard errors ranging from 0.39 to 1.33 mm across observers. Accuracy of placement for horizontal fibrils was substantially worse, however, with standard errors ranging from 1.87 to 4.19 mm.

This difference can be understood in terms of the information provided to the visual system. For the verti-

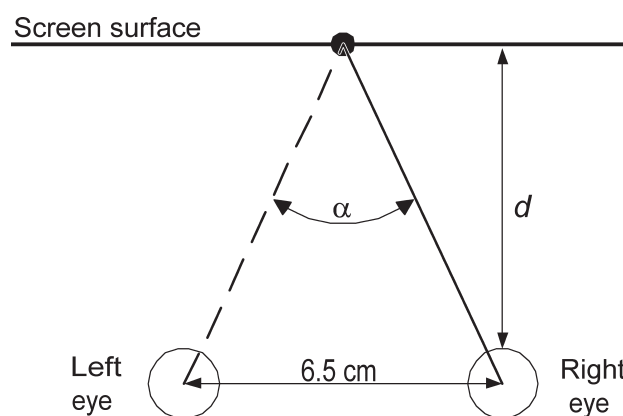


Figure 9. Illustration of the variables that determine the “correct” viewing distance by the observer, in which perceived depth is the same as the actual depth within the imaged object.

cal fibrils, every point along the length of the fibril contributes corresponding points on the two retinas that exhibit horizontal disparity. The longer the fibril, the more points there are to contribute depth information. On the other hand, for the horizontal fibrils, the only truly identifiable points that will produce horizontal disparity are the two ends of the fibril. For intermediate points, the visual system will have a hard time identifying corresponding points in the two retinal images because they are indistinguishable. The implication is that a radiologist will be much better at determining the depth of objects in stereo radiographs that have a lot of vertical structure and will be less able to determine the depth of objects that have predominantly horizontal structure. This also means that if one constructs a three-dimensional cursor that can be moved in depth, it should have strong vertical components.

AN APPLICATION OF STEREO IMAGING: STEREOSCOPIC DIGITAL MAMMOGRAPHY

A preliminary project has recently been completed to evaluate the contribution of stereo mammography in the diagnosis of breast cancer (17). During a period of several years, we acquired both standard film and stereo digital mammographic images of the breasts of a number of women scheduled for biopsy of a suspicious focal breast lesion. The stereo mammograms were acquired with a preclinical version of a digital mammography unit, with a 6° shift in the x-ray tube between exposures while the detector and breast remain fixed in position. An illustrative stereo pair of digital mammograms is shown in Figure 10. We conducted a reading study to determine the diagnostic accuracy achieved with standard film alone compared to the diagnostic accuracy achieved with standard film read together with the stereo mammogram. A second goal, which was added as the project progressed, was to obtain preliminary data on the capability of stereo

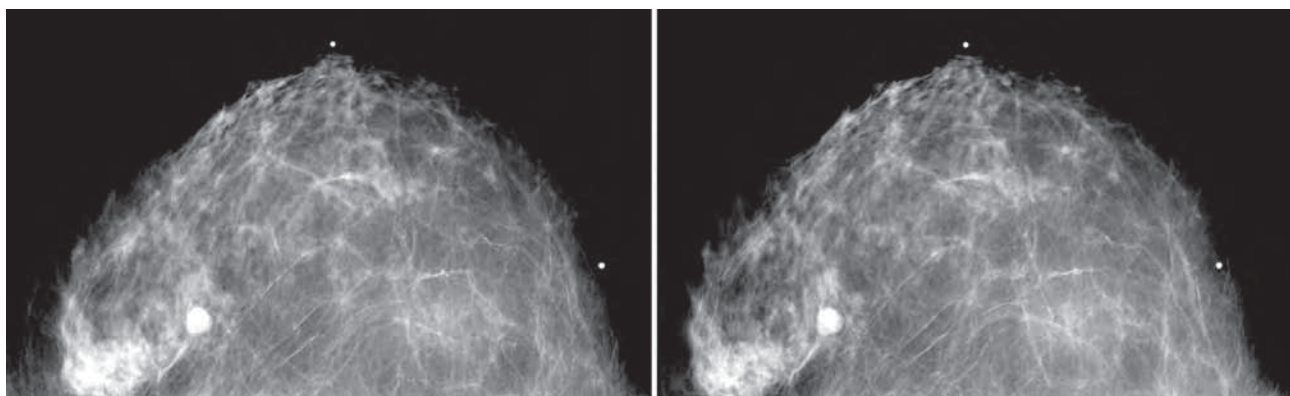


Figure 10. Stereo pair of digital mammograms acquired on a preclinical version of a digital mammography unit. The x-ray source was rotated by 6° between the two exposures ($\pm 3^\circ$ either side of the perpendicular to the detector surface). Although the two images look similar, different amounts of horizontal parallax are present for corresponding points at different depths in the imaged breast tissue. It is possible to experience the fused stereo image by crossing one's eyes. A benign mass is seen on the mammogram at 8 o'clock. When viewed in stereo, the location and orientation in depth of the many strands of fibrous tissue and vessels become readily apparent.

mammography to depict subtle lesions that are not visible on the corresponding standard films.

The reading study was conducted with five experienced mammographers individually reading the images from 129 pathologically proved cases with 137 malignant and benign lesions (several patients had more than one lesion). The reading of each patient's images was conducted in two successive stages. The reader first examined the full set of film mammograms from the diagnostic study that led to biopsy, rating the probability that the lesion was malignant on a scale of 0–100. The reader was then shown the stereo view of the lesion and asked to rate the probability of malignancy again. The stereo images were viewed on a stereo display workstation capable of displaying the entire digital mammogram ($2,304 \times 1,800$ pixels) at half resolution or a $1,024 \times 512$ region of interest centered around the lesion at full resolution. The stereo image was always a craniocaudal view acquired just before biopsy. For each case, the reader was also asked to report any additional lesions seen in either the films or the stereo mammogram, in addition to the known lesion subjected to biopsy.

We conducted a receiver operating characteristic-based analysis of the accuracy of the readers' ratings of the likelihood of malignancy for the two viewing conditions. Diagnostic accuracy, which was measured with A_z (area under the receiver operating characteristic curve), was 0.83 when readers viewed the films alone and increased to 0.86 when they also viewed the stereo mammogram, a statistically significant improvement ($P < .01$).

Perhaps a more important finding was that readers detected a considerable number of likely new lesions with the stereo mammograms, lesions that were not detected in the films. In all, 39 new lesions were reported in the 129 cases, corresponding to 30% of the cases. Of these 39 lesions, 30 were reported as masses,

six as new calcification clusters, and three as architectural distortions. Although we do not have independent truth for many of these newly detected lesions, we do have truth for one subset: masses detected only in the stereo mammogram in association with prior film-detected calcifications. For 11 of 12 such cases, the pathology report stated that the calcifications were located within a mass (most often a fibroadenoma).

As a follow-up, we are now beginning a large clinical study of stereoscopic digital mammography, funded by the US Army's Breast Cancer Research Program. In this study, 2,000 women at high risk for development of breast cancer will undergo digital screening mammography, including stereo imaging. We will compare independent readings of the images from each case performed by different mammographers with stereo and standard nonstereo reading conditions. The hypothesis is that stereo imaging will lead to earlier detection of small subtle lesions and, by increasing the confidence of the reader, to a reduced rate of recall of patients for further work-up.

DOUBLE THE X-RAY DOSE WITH STEREO IMAGING?

On the face of it, it would seem that the total x-ray dose to acquire a stereo pair of digital radiographs would be twice the dose of a single nonstereo digital radiograph. Each image in a stereo pair, however, represents an independent sampling of x-ray quantum mottle. When the visual system of the observer fuses the two images into a single cyclopean perception, it is possible that quantum noise in the fused image will be reduced compared with that of a single nonstereo radiograph. In fact, signal detection theory suggests that the signal-to-noise ratio of the fused image may be increased by the square root of 2 because of the independence of the quantum noise in the two images.

The theory suggests that the x-ray dose per image might be reduced by half while still maintaining the same level of detectability as the single nonstereo radiograph.

Maidment (31) and his colleagues have performed several contrast-detail studies using digital images of a mammographic phantom acquired at different exposures to test this hypothesis. Five observers viewed these images on a monitor while wearing stereo LCD glasses. For the nonstereo reading condition, the same image was presented to both eyes; for the stereo reading condition, a stereo pair of images was viewed stereoscopically. Of importance, the stereo pair was acquired with no angular separation between the two exposures, so that no depth was seen when the pair was viewed stereoscopically. This was done to remove the possibly confounding effect that depth would have introduced into the detection of details. Maidment (31) wished to test only the effect of independent samples of quantum noise seen by each eye on the ability to detect details in the images.

One result was that, for a fixed x-ray exposure level, more details were seen in the stereo images than in the nonstereo images, as predicted by signal detection theory. A second conclusion was that the total dose needed to produce a stereo pair of images with detectability of details equal to that of a single nonstereo image was only 1.1 times the dose used for the nonstereo image. Thus, it may be that, depending on the signal-to-noise ratio needed for a particular diagnostic task, the total x-ray dose for a stereo radiographic pair of images may not need to exceed that of a single nonstereo image by much. Of course, this is not taking into account the considerable benefit that may be provided by seeing the imaged object in depth.

BIPLANE CORRELATION IMAGING

Stereo pairs of x-ray images have been used for other things besides in-depth visualization of human organs. For example, stereo pairs of digital mammograms, acquired with a separation angle of 30° , have been used for some time in stereotactic biopsy systems. The large separation angle permits precise localization of an abnormality in the breast tissue, enabling placement of a guide wire into the abnormality. In this case, however, the radiologist does not ever view the two images stereoscopically and, in fact, would be unable to fuse the two images because of the large separation angle. Instead, the radiologist identifies the location of the abnormality in each of the two planar images, and a computer determines the three-dimensional coordinates of the abnormality from those two locations.

Samei et al (32) have recently proposed another nonstereoscopic use for stereo pairs of x-ray images. In recent years, a number of systems have been devel-

oped for computer-aided detection (CAD) of abnormalities in the breast and the lungs as a means of aiding radiologists in the detection of subtle abnormalities. A limitation of these systems is that they often identify a considerable number of false-positive lesions because of superimposed normal anatomic structures. These false-positive findings require individual examination and rejection by the radiologist. These investigators (32) reasoned that the false-positive rate could be reduced if one acquired a stereo pair of images separated by a small angle and then cross-correlated the detections for each of the two images. Only those candidate lesions seen in the same area in both images would likely be true positives. Other candidate lesions seen in only one image would most likely be the result of chance superposition seen from that particular point of view and could be rejected.

Samei et al (32) acquired pairs of digital posteroanterior and oblique radiographs of the lung, separated by varying angles. They applied CAD processing to each image to detect subtle lung lesions and then eliminated likely false-positive findings by applying a cross-correlation rule between the two views. They found that 3° of separation between the two views was optimal and that although detection sensitivity was reduced by about 20% from single-view CAD, the false-positive rate per image was about 94% less than that of single-view CAD. The relative improvement in false-positive reduction was higher for smaller nodules. The positive predictive value improved by 140%. Thus, the use of biplanar views in CAD dramatically reduced the false-positive rate and improved the positive predictive value.

In conclusion, we have witnessed the rapid emergence of digital radiographic techniques in recent years. We have also seen the equally important companion development of high-resolution, high-performance digital soft-copy displays. The combination has led to renewed interest in stereoscopic viewing of radiologic images, with application in many areas of radiology.

As one example, in the past several years, important advances have been made in the quality and speed of software applications that provide volume renderings of volumetric data sets, such as those captured by CT and MR imaging (33). In the past, this type of image processing was performed on separate specialized workstations. Now, many equipment manufacturers are beginning to incorporate this capability directly into the viewing stations attached to the imagers. Currently, an observer senses the volumetric shape of rendered surfaces through monocular visual cues such as shading and highlighting of the surface and through dynamic rotation of the point of view. Stereo imaging offers a potentially useful extension to this capability. To see a rendered volume as a stereo image in depth, the software need only compute images seen from two points of view, separated horizontally by about 6° , and present these two images on a stereo display work-

station. With sufficient computing power, the observer could fly the general point of view around in the imaged volume, providing a "magic carpet" tour of the rendered surfaces.

Stereoscopic image acquisition and display should be relatively easy and inexpensive to implement in the newly emerging digital radiographic systems. For example, there is currently considerable research interest in tomosynthesis of the breast. The modifications of the digital mammography unit needed for tomosynthesis are exactly those needed for stereo image acquisition, namely, an ability to move the x-ray source automatically through a succession of small angular offsets, obtaining an exposure after each movement.

A number of medical research groups are now pursuing research on stereoscopic imaging in radiology. We may expect interesting progress from them in the next several years.

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2.3: Invited Paper: Stereoscopic Digital Mammography

David J. Getty

BBN Technologies

10 Moulton St., Cambridge, MA, USA 02138

getty@bbn.com

Abstract: *Stereo mammography holds the promise of improving the early detection of breast cancer by providing the radiologist with a volumetric view of the breast. In a preliminary study, stereo mammography was shown to significantly improve diagnostic accuracy, and also revealed a number of lesions that were not detected in corresponding 2D film views. A clinical trial now underway at Emory University, will compare stereo digital mammography to non-stereo digital mammography in a screening context, for improved sensitivity and accuracy of lesion detection and for reduced rate of patient recall.*

Keywords: Stereoscopic imaging; stereoscopic display, digital mammography; breast cancer; lesion detection.

Introduction

Mammography, in its standard form requiring the reading of two orthogonal 2D views, is widely regarded as one of the most difficult radiographic exams to interpret. Subtle lesions may be masked by superimposition of overlying or underlying normal breast tissue, and thus be undetectable. The need to confirm a possible lesion seen in one view on the second, orthogonal view is also very problematic. Even when a lesion is confirmed on both views, understanding its three-dimensional shape and characteristics from these views can be difficult, particularly for clusters of micro-calcifications (small dots of calcium, on the order of 100-200 μm in diameter) where finding a one-to-one correspondence of elements is usually not possible.

Stereoscopic digital mammography holds the promise of significantly reducing these problems. In a stereo mammogram, the radiologist is provided with a stereoscopic x-ray view of the breast, in which a subtle lesion is directly seen volumetrically, separated from overlying and underlying normal tissue in depth. A true lesion can be confirmed in a single stereo view, at a particular locus and orientation within the breast. Moreover, the volumetric shape of a mass or architectural distortion, and the geometric structure of clustered calcifications, can be directly appreciated, without the need for mental reconstruction from the two separate 2D views.

Acquisition of a Stereo Mammogram

A stereo mammogram consists of two x-ray images of the breast taken sequentially from slightly different points of view. As illustrated in Figure 1, the x-ray source is rotated by 6 to 10 degrees between exposures while the position of the x-ray detector and the breast remain fixed in position. The digital detector captures each x-ray image directly and

stores it as a data file on a computer. In the research reported here, stereo mammograms were acquired on a GE Senographe® 2000D full-field-of-view digital mammography unit that had been modified to permit off-axis images to be acquired.

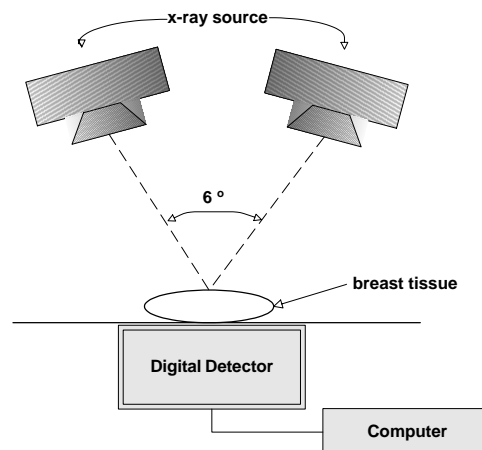


Figure 1. Acquisition of a stereoscopic digital mammogram.

An example of a stereo pair of digital mammograms containing a benign mass is shown in Figure 2. Although the two views look very similar, there are subtle differences in the two images resulting from their having been captured from slightly different points-of-view. When one image is presented in isolation to each eye, the visual system is able to fuse the two images into a single image seen in depth. (It is possible to experience this here crudely by crossing your eyes and concentrating on the middle image of three that you will see).

Display of a Stereo Mammogram

Several different methodologies are available for display of stereo mammograms. Regardless of the methodology employed, the requirement is that each of the two images that comprise the stereo pair be uniquely channeled to one, and only one, eye.

Temporally-Multiplexed Stereo Displays. One class of stereo display systems utilizes time-multiplexed display of the stereo pair. The two images are presented alternately in rapid succession—typically at a 120 Hz frame rate—on a single display monitor. The user wears special stereo-viewing glasses whose lenses are LCD shutters. The stereo-viewing glasses are synchronized to the display and alternately block each eye's view of the display as the two images are displayed alternately—effectively routing each

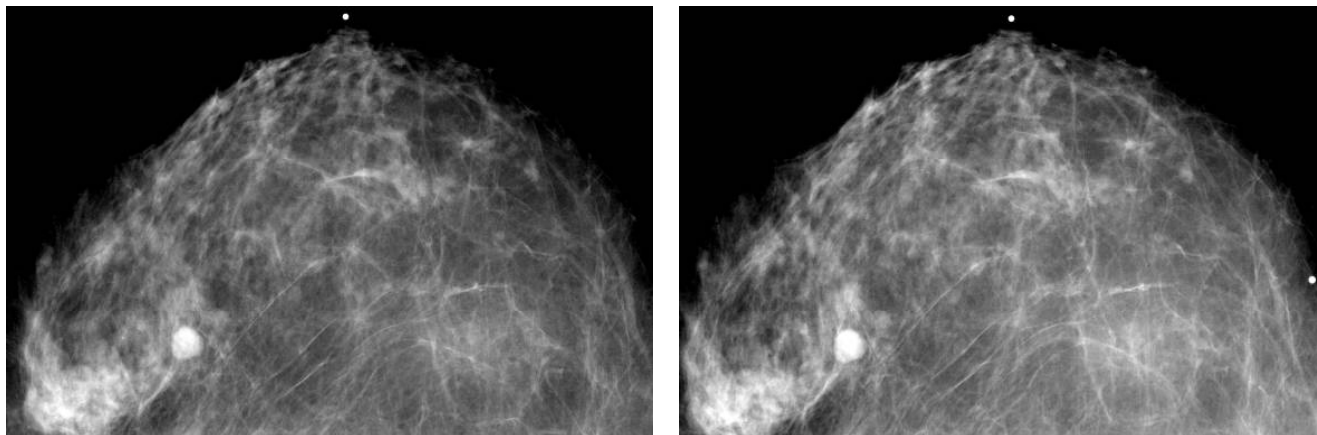


Figure 2. Stereoscopic pair of digital mammograms, with a benign mass located at about 8 o'clock. It is possible to see the images in depth by crossing your eyes and attending to the central image.

image to only one eye. The user's visual system fuses the two images into a single image seen in depth. We used this method of stereo display in our earlier research. Stereo mammograms were presented on a high-resolution (2K x 2K), monochrome MegaScan CRT monitor, and viewed using StereoGraphics CrystalEyes® stereo glasses, shown in Figure 3.

Spatially-multiplexed Stereo Displays. Another class of stereo display systems conveys the two images to the two eyes simultaneously through spatially separate channels. There are a number of different technologies for accomplishing this. One example is the Planar SD5000 stereo display which is based on the Fergason Stereo Mirror concept [1]. In this system, shown in Figure 4, two high-resolution (2.5K x 2K), monochrome LCD flat panel monitors (C5i) are mounted one above the other, with a 120-degree angle separating the two surfaces. The image emitted from the upper monitor is polarized in one direction while the image emitted from the lower monitor is polarized in the orthogonal direction. A "half-silvered" glass plate is mounted between the two monitors, bisecting the angle between them. The user wears lightweight

passive polarized glasses, with the Left and Right lenses polarized orthogonally, such that the user's Right eye sees only the image on the lower monitor, transmitted through the glass plate, and the user's Left eye sees only the image on the upper monitor, reflected from the coated glass. The perceptual result is a single fused image, seen in depth. This display system will be used in a clinical trial of stereo digital mammography just now underway at Emory University. The advantages of this system over our earlier CRT-based system are (1) a much brighter display (luminance of the LCD monitor is 500 cd/m²; luminance of the CRT monitor was 150 cd/m²), and (2) lightweight passive polarized glasses instead of the heavier, shuttering polarized LCD glasses. The one disadvantage of this spatially-multiplexed system is a greater sensitivity to loss of the stereo depth effect with head tilt. With the passive glasses, as the user's head is tilted away from vertical, the polarization axes of the two lenses rotate away from horizontal and vertical, allowing leakage into each eye of the image intended only for the other eye. This problem does not arise with the temporally-multiplexed systems.



Figure 3. Temporally-multiplexed stereo display.



Figure 4. Spatially-multiplexed stereo display.

Control of the Displayed Stereo Image

Horizontal Parallax. Because the two images of a stereo pair are acquired from slightly different points of view, the location of a particular object in the two images will be separated horizontally, by an amount that depends directly on the location of the object in depth. There are three types of parallax, illustrated in Figure 5. If a point belonging to an object is displayed at exactly the same position in the left- and right-eye images, then it is said to have “zero parallax.” The perceptual effect is that the object is seen to lie at the surface of the display screen.

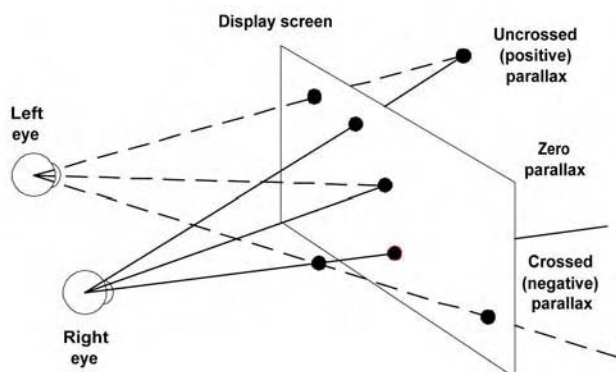


Figure 5. Illustration of uncrossed, zero, and crossed parallax of pairs of corresponding points shown on a single display screen.

In the other two cases, a point belonging to an object is displayed at different locations in the left- and right-eye image. If the right-eye point is displaced to the right of the left-eye point, then the object will be perceived to lie behind the screen surface. The larger the separation, the farther the object will be from the screen surface. This case is called “uncrossed” or “positive” parallax. In the third case, if the right-eye point is displaced to the left of the left-eye point, called “crossed” or “negative” parallax, then the object will be perceived to lie in front of the display surface. Again, the larger the separation, the farther the object will be from the screen surface, towards the observer.

Inversion of Displayed Depth. While the stereo point-of-view of the imaged object is predetermined by the point-of-view at the time of image acquisition, there are two other aspects of the viewed volume that the user can manipulate [2]. First, one can invert depth by swapping the two images—presenting the left-eye image to the right eye and the right-eye image to the left eye. Consider the two points corresponding to uncrossed parallax in Figure 5. When we swap the images, as shown in Figure 6, the dot previously seen by the left-eye is now seen by the right-eye, and vice versa. So now we have crossed parallax and the object will be seen not behind the screen, but in front of it. Similarly, dots originally displaying crossed parallax will now have uncrossed parallax. Thus, objects originally seen in front of the screen will now be seen behind it, and vice versa.

Dots with zero parallax will still have zero parallax, and remain seen at the screen surface. Thus, the effect of swapping images is to invert depth—much like reaching into a glove and pulling it inside out. If, in addition to swapping the two images, one also spins each image 180 degrees about a vertical axis, then the inverted depth image is seen as if one had walked around the object to view it from the backside.

Inverting depth can be important in stereo viewing, especially of stereo mammograms. It is easier to attend to objects seen in the foreground compared to those seen in the background, especially when there is a clutter of objects in the foreground. By allowing a radiologist to invert depth, tissue originally at the back of the displayed volume can be moved to the front of the volume, making it easier to perceive and inspect.

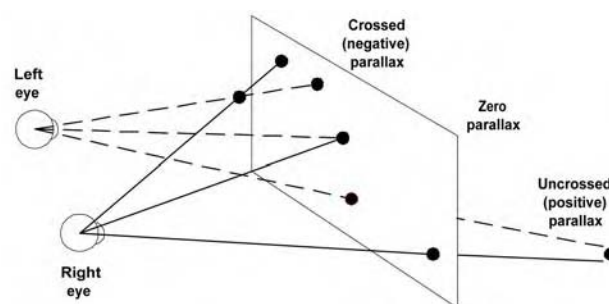


Figure 6. Inversion of perceived depth, achieved by swapping the two images between eyes.

Shifting Location of the Displayed Volume. A second aspect of the viewed volume that can be manipulated is the location of the displayed volume in depth with respect to the screen surface. If one shifts the right-eye image slightly to the left while holding the left-eye image fixed, as shown in Figure 7, then the horizontal parallax of all points will be changed in the direction of uncrossed parallax. Points originally with uncrossed parallax will have larger

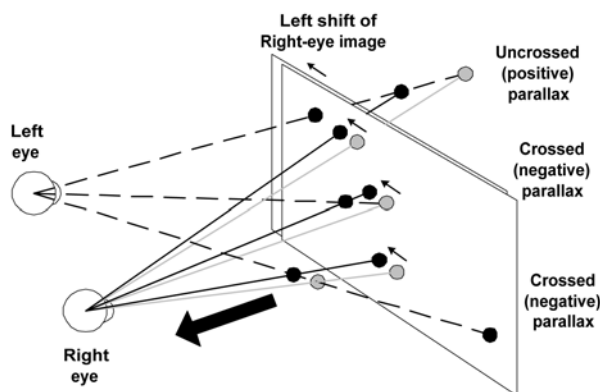


Figure 7. Shifting location of the displayed volume uncrossed parallax, and points with crossed parallax will have decreased crossed parallax. The perceived effect is to shift the entire viewed volume forward in depth, towards

the observer, with the amount of shift in depth proportional to the amount of left lateral shift of the right-eye image. Shifting the right-eye image in the other direction, to the right, will shift the viewed volume away from the viewer relative to the screen surface. It is only the amount of relative shift of the two images that matters, so one could just as well make shifts to the left-eye image, or to both. In fact, splitting a desired amount of shift between the two images will minimize the amount of stereo image lost at the left and right edges of the display.

Control of location of the viewed volume is useful in that many people initially find it difficult to perceive a displayed volume that begins at the screen surface and comes towards one in space. Usually, they are more comfortable with a displayed volume that starts at the screen surface and goes back into the monitor. It's always possible to achieve this condition by using relative shifts of the two images. On the other hand, with increasing experience, people often come to prefer a displayed volume that comes out into space.

Stereo Cursor. A stereo cursor is useful for allowing a user to point out a region of interest in the stereo image, in depth, to another user. If one draws a cursor icon in both images of the stereo pair at the same location then there is no horizontal parallax and the cursor is seen to lie at the surface of the display screen. If the icon is drawn with horizontal separation in the two images, then the cursor is perceived to lie either in front of the screen (for crossed parallax) or behind the screen (for uncrossed parallax), with depth proportional to the amount of separation.

Results of a Preliminary Study of Stereoscopic Digital Mammography

A preliminary study has recently been completed to evaluate the contribution of stereo mammography in the diagnosis of breast cancer [3]. We acquired both standard film and stereo digital mammographic images on a number of women scheduled for biopsy of a suspicious focal breast lesion. The stereo mammograms were acquired on a pre-clinical version of the GE Senographe® 2000D digital mammography unit, with a 6-degree shift in the x-ray tube between exposures. We conducted a reading study to determine the diagnostic accuracy achieved by standard film alone compared to standard film read together with the stereo mammogram. A second goal, added as the project progressed, was to obtain preliminary data on the capability of stereo mammography to detect subtle lesions that were not visible in the corresponding film studies.

The reading study was conducted with 5 experienced mammographers individually reading 129 path-proven cases containing 137 malignant and benign lesions (several cases had more than one lesion). The reading of each case was conducted in two successive stages. The reader first examined the full set of film mammograms from the diagnostic study that led to biopsy, rating the probability that the lesion was malignant on a scale of 0 to 100. The

reader was then shown the stereo view of the lesion and asked to again rate the probability of malignancy. The stereo image was always a CC view acquired just prior to biopsy. For each case, the reader was also asked to report on any additional lesions seen in either the films or the stereo mammogram, in addition to the known, biopsied lesion.

We conducted an ROC-based analysis of the accuracy of the readers' ratings of the likelihood of malignancy for the two viewing conditions. Diagnostic accuracy, measured by Az (the area under the ROC curve), was 0.83 when the readers viewed the film study alone, rising to 0.86 when readers also viewed the stereo mammogram. This is a statistically significant improvement.

Perhaps a more important finding was that readers detected a very significant number of likely new lesions in the stereo mammogram—ones that were not detected in the films. In all, 39 new lesions were reported in the 129 cases, corresponding to 30% of the cases. Of these 39 lesions, 30 were reported as masses, 6 as new calcification clusters, and 3 as architectural distortions. While we do not have independent truth for many of these newly detected lesions, we do have truth for one subset: masses detected only in the stereo mammogram in association with prior film-detected calcifications. Of 12 such cases, the pathologic report for 11 of the 12 cases reported that the calcifications were located within a mass (most often a fibroadenoma).

A Clinical Trial of Stereoscopic Digital Mammography

We are now beginning a large clinical study of stereoscopic digital mammography at the Emory Breast Clinic, funded by the Army's Breast Cancer Research Program. In this study, about 2000 women at elevated risk for development of breast cancer will receive both standard (non-stereo) digital screening mammograms and a stereo digital mammogram. We will compare independent readings of each case, conducted by different mammographers, in stereo and standard, non-stereo reading conditions. We hypothesize that stereo imaging will lead to earlier detection of small, subtle lesions and will, by increasing the reader's confidence, result in a reduced rate of recall of patients for further work up.

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Clinical applications for stereoscopic 3-D displays

David J. Getty
Patrick J. Green

Abstract — Stereoscopic 3-D digital imaging holds the promise of improving the detection, diagnosis, and treatment of disease as well as enhancing the training and preparation of medical professionals through use of stereoscopic 3-D displays in concert with the many volumetric visualization techniques/modalities developed in recent years. While so-called 3-D graphics have improved the state of computer visualization in general, 3-D displays make full use of the human-visual perception, and thus can provide critical insight in complex computer-generated and video 3-D data. The stereo 3-D applications reviewed in this paper include screening of breast cancer and diabetic retinopathy, visualization for minimally invasive surgery, and the teaching of anatomy. Also included is a discussion of ground-breaking results from a stereo digital mammography clinical trial under way at Emory University.

Keywords — Steroscopic imaging, stereoscopic display, 3-D display, stereopsis, 3-D imaging, digital mammography, breast cancer, lesion detection, teaching anatomy, diabetic retinopathy.

1 Introduction

Advancements in computer graphics and volumetric presentation of data currently allow increasingly complex images to be presented in great detail. Translating these complex data into usable information in a timely fashion presents a significant challenge to the professional analyst of these images. This issue is particularly critical for medical imaging where an interpretation can have life and death implications. Furthermore, the increasing pressure on medical professionals to control cost makes the pursuit of efficiency in the delivery of results based on medical imaging an important goal as well.

In most computer-graphics applications, sophisticated algorithms use 2-D depth indicators such as relative size, interposition, perspective, and light shading to enhance the perception of depth. However, these widely used monoscopic depth cues, commonly referred to as comprehensively presenting a “3-D” view, do not employ the most powerful source of human depth perception. This process, called stereopsis, results from the fact that our two eyes received slightly different images of a scene because of their horizontal separation. The visual system detects these differences and translates them into perception of depth (see Fig. 1). This subconscious mental process was first described by Wheatstone in 1839.¹ Interest in stereoscopic imaging has existed since the birth of photography in the 1840s.

Many of the advantages of stereoscopic viewing were appreciated very early in the development of radiography. Only a few months after the discovery and public disclosure of x-rays by Röntgen in 1895, there appeared an article by E. Thomson describing the acquisition and viewing of stereoscopic x-ray images.² The medical value of stereoscopic x-ray imaging for localization of tissues and seeing

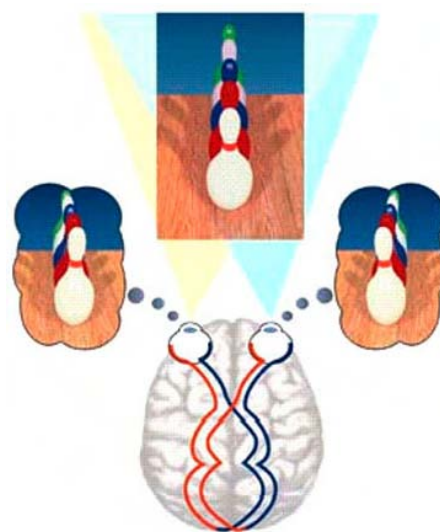


FIGURE 1 — The mental process of stereopsis.

structures in depth was soon appreciated by Sir James Mackenzie Davidson, a prominent British physician, who published an article in the *British Medical Journal* in 1898,³ and later, in 1916, published a book containing many illustrative stereo x-rays that demonstrated the utility of stereoscopic x-ray imaging.⁴

That so little time passed between the discovery of x-rays and the creation of the first stereoscopic x-ray images is not so surprising when one considers that stereoscopic photography was a very popular pastime at the beginning of the last century. It was commonplace for a family to own a parlor version of Holmes' stereoscope,⁵ an adaptation of an earlier stereoscope developed by Brewster in 1849.⁶ Printed stereo cards provided dramatic in-depth views of places and people from around the world. A modified form of these

D. J. Getty is with BBN Technologies, Cambridge, MA, U.S.A.

Patrick J. Green is with Planar Systems, Technology Group, 1195 NW Compton Dr., Beaverton, OR 97006, U.S.A.; telephone 503/748-5835, fax 503/748-1244, e-mail: pat.green@planar.com.

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viewers was also used in medical schools for teaching of anatomy.⁷

During the early part of the 20th century, devices were developed to aid the radiologist in viewing a stereo pair of x-ray images. This process was awkward and, because it was difficult to align the films precisely, the radiologist often experienced some amount of discomfort and eyestrain in using the device. Nevertheless, the added value of seeing the imaged tissue and anatomy in depth was such that stereo x-rays remained a commonly used technique in radiology departments until the advent of serial “slice”-based x-ray techniques, such as CT (computed tomography) and MRI (magnetic resonance imaging). Over the years, stereoscopic imaging has been applied, to advantage, to many different parts of the human body, including the brain,⁸ the hand and wrist,⁹ the rib cage,¹⁰ the breast,^{11,12} the lungs,¹³ and the vascular system.¹⁴

In recent years, the development of digital radiography, high-resolution digital display systems, and high-quality stereo viewing devices has made possible the development of medical stereoscopic imaging techniques that do not suffer from the limitations of the earlier film-based methods. For example, a stereo pair of digital x-ray images can be acquired easily and displayed to the radiologist in a manner that assures precise image registration and provides superb perception of depth in the imaged volume without visual strain. Furthermore, the digital display permits the radiologist to control and manipulate several viewed aspects of the stereo image (*e.g.*, gray-scale window level and window width, inversion of gray-scale, and inversion of depth) that can greatly enhance the value of the stereo imaging. This freedom is available in other medical modalities as well.

However, until recently, the additional computing burden and lack of suitable content and the ability to visualize it have made the everyday professional medical use of stereo 3-D visualization difficult and of limited productivity. These factors have largely been eliminated with the availability of affordable and powerful personal computers, the explosion of volumetric data, and the development of more-suitable and user-friendly stereoscopic 3-D displays. Viewing of imagery in 3-D offers the possibility of providing more efficient and potentially more accurate extraction of information and can provide a more realistic experience than conventional monoscopic viewing.

One of the oldest professional uses for stereoscopic 3-D imaging, both film-based and digital, has been in photogrammetry, the extraction of geospatial information from aerial and/or satellite image data. This discipline has fully embraced the benefits of stereoscopic 3-D imaging.¹⁵ Here, the ability to view topography in three dimensions allows the analyst to more quickly comprehend the relative placement of features on the ground and to accurately make measurements and judgments from complex visual data. As a simple example, the use of 3-D analysis potentially can clarify the ambiguity that might otherwise exist in determining whether a ground feature was concave or convex in a

2-D presentation. Use of stereoscopic 3-D imaging permits comprehension of more complicated spatial relationships that would be difficult or impossible to decipher in a 2-D analysis only. These same advantages of both improved efficiency and accuracy with the use of 3-D imaging can be applied to the analysis of complex medical images as well.

Volumetric 3-D displays^{16,17} offer a capability similar to stereoscopic 3-D monitors in making use of stereopsis-based depth perception. These displays can provide attractive user attributes such as spatial 3-D depiction of medical images and enhanced collaboration due to multi-user viewing. However, their high cost, potential artifacts, and limited resolution have inhibited widespread clinical use. This paper will focus on the more widely used stereoscopic 3-D display technology for medical applications.

2 Stereoscopic 3-D display overview

Providing a stereo pair of high quality images to a user has proven to be a challenging display-design exercise. While CRTs have dominated historically, the more recent introduction of new image engines based on AMLCDs and MEMS technology has created a resurgence of new stereo 3-D display designs. Performance attributes pertinent specifically to stereo 3-D displays include:

Parameter	Comment
Image quality	Not degraded from 2-D displays
Resolution in 3-D	Same as 2-D displays
Stereo crosstalk between left and right eye	Less than 1%
User comfort	Same as 2-D displays
Viewing angle	Same as 2-D displays, <i>i.e.</i> , multi-user
Luminance	Sufficient for use in normal room light
Screen size	Same as 2-D displays
Ease of interfacing	Same as 2-D displays
Ability to convert between 2-D and 3-D	Required
Footprint	Same as 2-D displays
Need for eyewear	None preferred
Cost	Market premium for 3-D displays

While no current stereoscopic 3-D display design provides adequate performance for all these parameters, there are stereo display designs with sufficient capability to have found consideration for clinical use. These displays create a stereo pair of images based on temporal, spatial, or polarization multiplexing. Time-based multiplexed displays using CRTs with fast-switching liquid-crystal shutters have been the most widely used 3-D displays. These present alternating left eye/right eye images frame sequentially at twice the typical refresh rate.¹⁸ Two approaches are commonly used. In one design, an LC shutter is placed in front of the CRT screen that switches between clockwise and counter-clockwise circular polarizations. Wearing passive, crossed circular polarizing glasses permits the segregation of the left eye/right eye images for stereo viewing. In the other approach glasses containing LC shutters as eyepieces are synchronized with the frame-sequential CRT presentation of the stereo images. The former design typically has low luminance, requiring use in a darkened room. The latter display

is prone to flicker which can cause discomfort. A significant logistical problem has arisen of late in that most of the CRT monitors used in these systems have gone end of life in their production due to the emergence of competitive AMLCDs for desktop monitor use. Both frame-sequential approaches are also employed in MEMS-based stereo 3-D projectors.¹⁹

So-called autostereo displays provide a spatial separation of the stereo image pairs through use of a converging pair of optical paths (one for each eye) that project the stereo images to a specific location relative to the display. When the user's eyes are positioned appropriately in this location, stereopsis is stimulated and 3-D stereo is perceived. This is accomplished using either an AMLCD with a lenticular lens²⁰ or a parallax barrier²¹ or two separate optical paths with a pair of image sources.^{22–24} The primary advantage of this approach is no eyewear is required. The designs using the parallax barrier or lenticular lens place these optical elements in the path of backlight illumination to create a separate left-eye and right-eye viewing zone spaced roughly at the interocular distance (the spacing of the eyes, ~6 cm) at a typical viewing distance. In both designs, stereo 3-D image pairs are thus generated at the expense of display resolution. In the autostereo designs where there is only a single viewing zone, the stereo 3-D viewing angle is severely restricted. It is possible to program the displays with several viewing zones to increase viewing angle, but this further reduces display resolution.²⁰ The autostereo displays based on dual light paths employ LCOS,²² AMLCDs,²³ or dual-CRT²⁴ image sources and separate optical paths. This design takes advantage of the excellent image quality of the respective display technology used where full resolution is made available in stereo. However, viewer head movement is typically restricted in order to maintain a stereo 3-D view and use is limited to a single user.

An additional variation on the dual-optical path approach is to use a head-mounted display where the miniature displays designated for each eye are driven with the stereo image pair. AMLCD²⁵ and OLED²⁶ miniature displays have been used. These have found use for minimally invasive surgery.²⁵

The polarized light-emitting nature of LCDs has been exploited for use in stereo 3-D displays. A relatively recent approach, called the StereoMirror™, combines the output of two AMLCDs into a 3-D image using a novel beamsplitter design.²⁷ The two AMLCDs are oriented at a fixed angle with the beamsplitter mirror bisecting the two monitors. This is shown in Fig. 2. The polarization in the reflective path is effectively rotated 90° with respect to its origin, and thus the stereo pair of images directed to the viewer has crossed polarization. This allows similarly crossed linear polarizing glasses to separate the stereo image. The design provides the flicker-free image quality at full resolution and attributes equivalent to 2-D AMLCDs. Since the display uses linear polarization, there is the possibility of increased stereo crosstalk with head tilt.



FIGURE 2 — Planar SD1710 StereoMirror™ monitor.

Another recent stereo 3-D display design making use of stereo separation based on polarization employs dual laminated AMLCDs where one panel modulates the pixel intensity and the other controls the distribution of light between the two eyes. A collimated backlight is used with circularly polarized eye glasses.²⁸ This design provides the form factor of a thin CRT with image quality comparable to that of AMLCDs.

3 Presentation of 3-D images

3.1 Control of the displayed stereo image

Horizontal parallax: Because the two images of a stereo pair are acquired from slightly different points of view, the location of a particular object in the two images will be separated horizontally, by an amount that depends directly on the location of the object in depth. There are three types of parallax, illustrated in Fig. 3. If a point belonging to an object is displayed at exactly the same position in the left- and right-eye images, then it is said to have “zero parallax.” The perceptual effect is that the object is seen to lie at the surface of the display screen.

In the other two cases, a point belonging to an object is displayed at different locations in the left- and right-eye image. If the right-eye point is displaced to the right of the left-eye point, then the object will be perceived to lie behind the screen surface. The larger the separation, the farther the object will be from the screen surface. This case is called “uncrossed” or “positive” parallax. The upper limit here is the discomfort level of the user in accommodating the degree

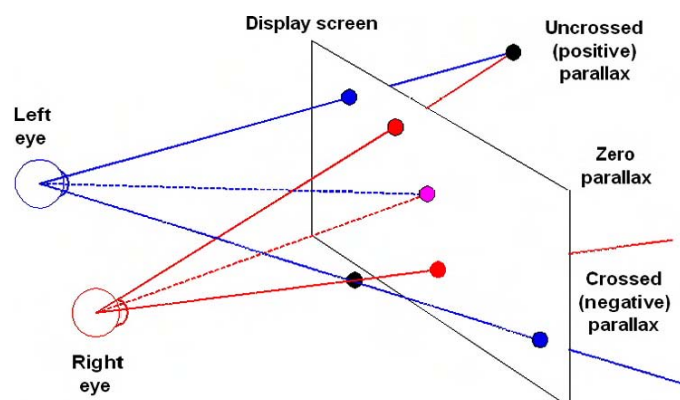


FIGURE 3 — Illustration of uncrossed, zero, and crossed parallax of pairs of corresponding points shown on a single display screen.

of separation. In the third case, if the right-eye point is displaced to the left of the left-eye point, called “crossed” or “negative” parallax, then the object will be perceived to lie in front of the display surface. Again, the larger the separation, the farther the object will be from the screen surface, towards the observer.

Inversion of displayed depth: While the stereo point-of-view of the imaged object is predetermined by the point-of-view at the time of image acquisition, there are two other aspects of the viewed volume that the user can manipulate.²⁹ First, one can invert depth by swapping the two images – presenting the left-eye image to the right eye and the right-eye image to the left eye. Consider the two points corresponding to uncrossed parallax in Fig. 3. When we swap the images, as shown in Fig. 4, the dot previously seen by the left eye is now seen by the right eye, and vice versa. So now we have crossed parallax and the object will be seen not behind the screen, but in front of it. Similarly, dots originally displaying crossed parallax will now have uncrossed parallax. Thus, objects originally seen in front of the screen will now be seen behind it, and vice versa. Dots with zero parallax will still have zero parallax, and remain seen at the screen surface. Thus, the effect of swapping images is to invert depth – much like reaching into a glove and pulling it inside out. If, in addition to swapping the two images, one also

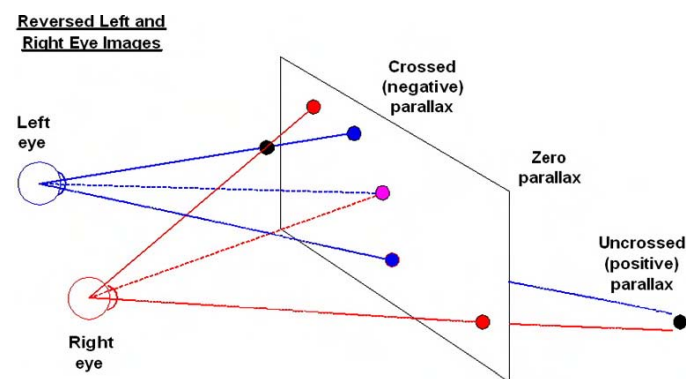


FIGURE 4 — Inversion of perceived depth, achieved by swapping the two images between eyes.

spins each image 180° about a vertical axis, then the inverted depth image is seen as if one had walked around the object to view it from the backside.

Inverting depth can be important in stereo viewing, especially of stereo mammograms. It is easier to attend to objects seen in the foreground compared to those seen in the background, especially when there is a clutter of objects in the foreground. By allowing a radiologist to invert depth, tissue originally at the back of the displayed volume can be moved to the front of the volume, making it easier to perceive and inspect.

Shifting location of the displayed volume: A second aspect of the viewed volume that can be manipulated is the location of the displayed volume in depth with respect to the screen surface. If one shifts the right-eye image slightly to the left while holding the left-eye image fixed, as shown in Fig. 5, then the horizontal parallax of all points will be changed in the direction of uncrossed parallax. Points originally with uncrossed parallax will have larger uncrossed parallax, and points with crossed parallax will have decreased crossed parallax. The perceived effect is to shift the entire viewed volume forward in depth, towards the observer, with the amount of shift in depth proportional to the amount of left lateral shift of the right-eye image. Shifting the right-eye image in the other direction, to the right, will shift the viewed volume away from the viewer relative to the screen surface. It is only the amount of relative shift of the two images that matters, so one could just as well make shifts to the left-eye image, or to both. In fact, splitting a desired amount of shift between the two images will minimize the amount of stereo image lost at the left and right edges of the display.

Control of location of the viewed volume is useful in that many people initially find it difficult to perceive a displayed volume that begins at the screen surface and comes towards one in space. Usually, they are more comfortable with a displayed volume that starts at the screen surface and goes back into the monitor. It's always possible to achieve this condition by using relative shifts of the two images. On the other hand, with increasing experience, people often

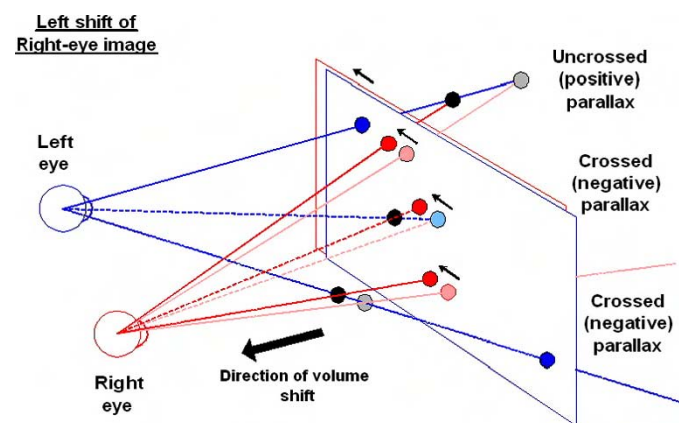


FIGURE 5 — Shifting location of the displayed volume.

come to prefer a displayed volume that comes out into space.

Stereo cursor: A stereo cursor is useful for allowing a user to point out a region of interest in the stereo image, in depth, to another user. If one draws a cursor icon in both images of the stereo pair at the same location then there is no horizontal parallax and the cursor is seen to lie at the surface of the display screen. If the icon is drawn with horizontal separation in the two images, then the cursor is perceived to lie either in front of the screen (for crossed parallax) or behind the screen (for uncrossed parallax), with depth proportional to the amount of separation.

3.2 Sources of digital 3-D content

Historically, one of the potential barriers for use of stereoscopic 3-D imaging in medicine has been the difficulty in obtaining and using suitable image content. There are at least three different methods for acquisition of stereo 3-D medical images. The most straightforward and historically the most common process is to simply acquire a stereo pair of images at a suitable small angle (3° – 8°) of stereo separation. Projection X-ray imaging is perhaps the most common modality for this process where the images are captured simultaneously or in as close succession as possible while the patient is immobile. For ophthalmic photography a fundus camera³⁰ is used and the stereo pair of images, either film-based or digital, is acquired simultaneously *via* a dual optical path in the camera.

Digital acquisition and processing technology allow two additional methods for creating stereo 3-D content. Tomographic imaging, such as MRI, CT, positron emission tomography (PET), and others provide 2-D set of slice data that can be rendered into a volumetric image using suitable software. Once the volumetric image has been rendered, viewing in stereo 3-D is accomplished by creating two views in software of the volumetric image, again with a small separation angle between the two images, and porting these two views to the appropriate data paths suitable for the particular 3-D display. Commercially available³¹ and open source³² software packages are available that function in this manner. Display interfacing is facilitated by the OpenGL³³ and DirectX³⁴ application programming interfaces (API) standards that support processing and handling of stereo 3-D image data.

A third possible approach to creation of stereo 3-D content involves using an existing 2-D image and creating a stereo pair view from it. This software process has been employed to convert 2-D movie films to stereo 3-D and makes use of knowledge of the distance to the image source and other acquisition parameters in the original view. The original image would be used as one view, *e.g.*, for left eye, and the synthesized view would be for the right eye. This technique is currently not employed widely for medical imaging. There would be potential legitimate concerns regarding the fidelity of the synthetic image.

4 Applications

4.1 Teaching anatomy

Probably the first medical use of 3-D imagery was for the teaching of anatomy using photographic stereo pairs taken of cadavers. The Edinburgh Stereoscopic Atlas of Anatomy⁷ was published as a collection of 250 plates containing stereo pairs of photographs with anatomical detail for the entire body. The perception of depth was achieved with the use of a special stereo viewer made either from metal or wood. The understanding of the three-dimensional relationships of various components in the body has historically been thought to provide important insight for a comprehensive medical education. Use of stereo 3-D viewing can be a useful resource when cadavers are in short supply or unavailable. Starting in the 1940s ViewmasterTM produced disks containing similar stereo 3-D anatomical photos for medical students who could visualize the human body using this familiar children's toy.³⁵ More recently, the Visible Human Project provides content that can be viewed in stereoscopic 3-D.³⁶

4.2 Digital mammography

Mammography is widely regarded as one of the most difficult radiographic exams to interpret. In a standard screening exam, two nearly orthogonal x-ray views are acquired of each breast. Each 2-D projection image is examined by the radiologist for suspicious focal abnormalities. False positive detections and false negatives are significant problems. False positives arise when normal dense tissue at different depths in the breast superimpose in a particular projection to mimic a mass. False negatives arise when subtle lesions are masked by superimposition of overlying or underlying normal breast tissue, and thus are undetectable. Radiologists attempt to confirm a possible lesion seen in one view on the second, orthogonal view, although this is often not possible. Even when a lesion is confirmed on both views, understanding its three-dimensional shape and characteristics from these views can be difficult, particularly for clusters of micro-calcifications (small dots of calcium, on the order of 100–200 μm in diameter) where finding a one-to-one correspondence of elements in the two orthogonal views is usually not possible.

Stereoscopic digital mammography holds the promise of significantly reducing these problems. In a stereo mammogram, the radiologist is provided with a direct in-depth view of the breast. False positives occur less frequently because layers of normal tissue at different depths in the breast are seen to lie at different depths, without superposition. False negatives occur less frequently because true focal abnormalities are seen as distinct from overlying or underlying tissue. Moreover, the volumetric shape of a mass or architectural distortion, and the geometric structure of clustered calcifications, can be directly appreciated without the need for mental reconstruction from the standard two 2-D views.

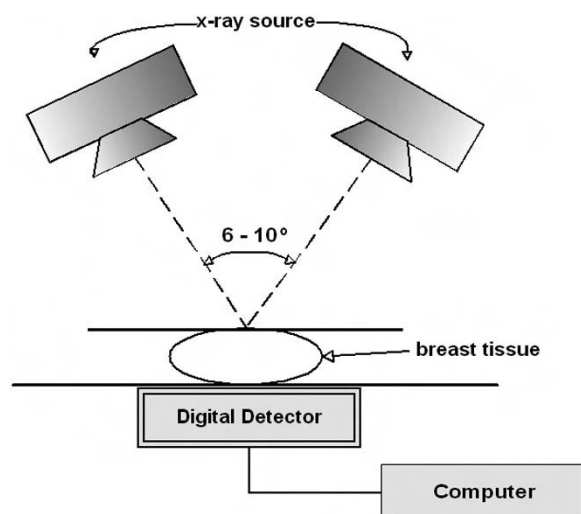


FIGURE 6 — Acquisition of a stereoscopic digital mammogram.

Acquisition of a stereo mammogram: A stereo mammogram consists of two x-ray images of the breast taken sequentially from slightly different points of view. As illustrated in Fig. 6, the x-ray source is rotated by 6–10° between exposures while the position of the x-ray detector and the breast remain fixed in position. The digital detector captures each x-ray image directly and stores it as a data file on a computer.

An example of a stereo pair of digital mammograms containing a benign mass is shown in Fig. 7. Although the two views look very similar, there are subtle differences between the two images resulting from their having been captured from slightly different points-of-view. When one of the two images is presented uniquely to one eye and the other image to the other eye, the visual system is able to fuse the two images into a single image seen in depth. (It is possible to experience this here crudely by crossing your eyes and concentrating on the middle image of three that you will see.)

A clinical trial of stereoscopic digital mammography: A clinical trial of stereoscopic digital mammography versus

standard digital mammography in a screening setting is currently under way at the Emory University Breast Imaging Center in Atlanta, Georgia.³⁷ To be eligible for admission into the trial a patient must be at elevated risk for development of breast cancer. To date, about 750 female patients have been enrolled in the trial. Each enrolled patient receives two screening mammographic exams, first a standard digital exam, and second a stereoscopic exam. The stereoscopic exam consists of the same two orthogonal views included in a standard screening exam, each view consisting of a stereo pair of x-ray images acquired with an angular separation of 10°. The standard and stereo examinations are read independently by two different mammographers. If either reader detects an abnormality, the patient is recalled for further standard (non-stereo) clinical work-up examination.

The interpretation of the acquired stereo pair is performed on a prototype version of the StereoMirror™ from Planar Systems. This display provides viewing of the stereo image pair at the 5-Mpixel resolution needed for a mammographic diagnosis. A picture of the monitor in use by one of the authors (DJG) is shown in Fig. 8.

The interim results from the trial are striking. In the current case sample, stereo mammography has reduced false-negative readings by 44% (27 false-negative readings by standard mammography, compared to only 15 by stereo mammography). While this result is only marginally statistically significant ($p < 0.09$), it does strongly suggest that stereo mammography is more sensitive than standard mammography in detecting true lesions.

Equally impressive, stereo mammography has reduced false-positive lesion detections in the current sample by 37% (68 false positive detections by standard mammography compared to only 43 for stereo mammography). This result is both statistically ($p < 0.02$) and clinically significant. The improvement in screening mammography that would be afforded by stereo mammography would relieve many women from the considerable stress and anxiety produced by unnecessary recalls, result in substantial annual financial

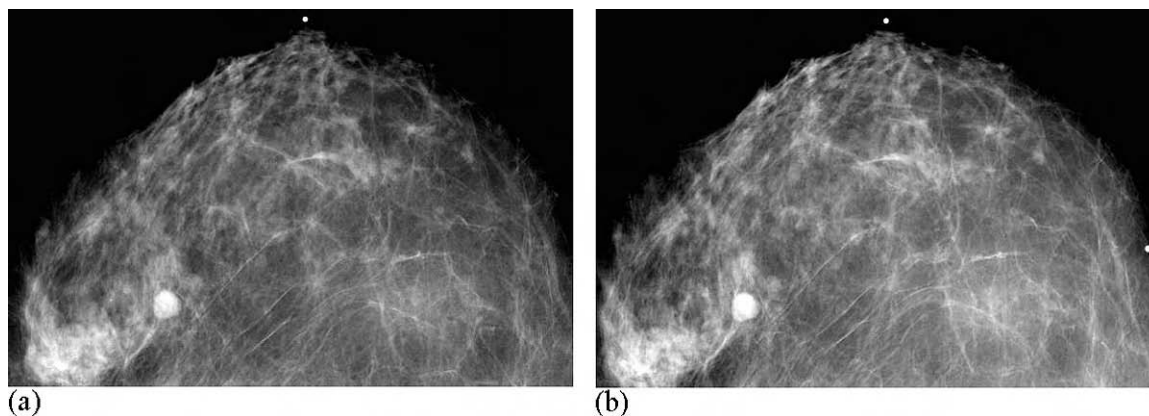


FIGURE 7 — Stereoscopic pair of digital mammograms, with a benign mass located at about 8 o'clock. It is possible to see the images in depth by crossing your eyes and attending to the central image.



FIGURE 8 — Use of a 5-Mpixel Planar StereoMirror™ monitor in the Stereo Digital Mammography clinical trial.

savings, and ease the load on already overburdened systems for screening mammography.

4.3 Tomography

Several well-established imaging modalities (*e.g.*, CT and MRI), as well as other newly developing modalities (*e.g.*, breast tomosynthesis and breast CT) produce a series of spaced 2D images, or “slices,” along an axis through the imaged tissue. The conventional method of viewing the volumetric data set resulting from such an exam is to display the individual 2D slices sequentially, often in a cine mode. Stereo display offers the possibility of a more efficient method of viewing the data set, by rendering a stereo pair of views, separated by a small number of angular degrees, of all or a subset of the slices. One particular advantage of stereo display is the gain of local context in depth, missing from any single 2D slice. Researchers are currently studying stereo display applied to spiral CT of the lungs¹³ and to breast tomosynthesis.

4.4 Diabetic retinopathy

According to the World Health Organization (WHO), the incidence of type 1 and type 2 diabetes is increasing rapidly worldwide.³⁸ Diabetic retinopathy (DR) is a complication of both forms of diabetes often progressing to a hemorrhaging in the retina that is a leading cause of blindness in the Western World. Ultimately, over 90% of people with type 1 diabetes and 60% with type 2 will develop diabetic retinopathy. Effective screening for DR has been proven in the Early Treatment Diabetic Retinopathy Study (ETDRS) to reduce the risk of severe vision loss with the proper detection and treatment.³⁹ Computer-modeling studies have suggested that if appropriate screening and subsequent treatment were employed, annual expenditures for more advanced treatment of \$250 to \$500 million would be saved.

A set of stereo 3-D views of the retina facilitates the evaluation of the abnormal blood vessels associated with DR and is considered a “gold standard” technique for diagnosis. The ETDRS standard protocol calls for acquisition of seven stereo image pairs for each retina using a fundus camera.³⁰ These images are then examined using a stereo 3-D display. Evidence of the importance of stereo imaging for this application is indicated by the fact that in 2004 the Digital Imaging and Communications in Medicine (DICOM) standard was amended to include accommodation for archiving the stereo pairs of images used in the diagnosis of DR.⁴⁰ Important traits for a stereo 3-D display used in this application are image quality, specifically resolution,⁴¹ and viewing comfort. In particular, minimizing user fatigue and discomfort is quite important since the ophthalmic readers can spend their entire work shift examining stereo retinal images.

4.5 Minimally invasive surgery

Use of minimally invasive surgical (MIS) procedures is growing rapidly because of the inherent improvement to patient outcomes by minimizing pain, reducing the risk of complications and hastening recovery time. Rather than viewing the procedure directly through a large incision, the operation is performed using tools inserted through natural or surgically prepared openings in the body. The surgeon visualizes the operation using a monitor with input taken from a video probe placed into the body. Because the physician does not directly view the surgical field, there is no depth perception unless a suitable stereo acquisition system and display is used. A stereo 3-D acquisition system provides separate left eye/right eye video channels that can be accomplished using a fiber-optic probe with dual optical paths and dual external cameras. More recently, a miniature camera has been developed suitable for providing stereo viewing inside the body cavity.⁴² Use of stereo 3-D visualization potentially provides the surgeon with a more-realistic viewing experience for the procedure that can improve surgical efficiency and reduce error. Stereo 3-D monitors must have regulatory approval for use in the operating room and be capable of displaying real-time stereo video.

The daVinci™ robotic surgical system (Intuitive Surgical Inc., Sunnyvale CA) makes use of a stereo 3-D workstation using dual CRTs with magnification as the visualization aide for a remotely guided surgical manipulator system.⁴³ This display immerses the surgeon in a 3-D video operating field. This system is being adopted for delicate prostate, gynecological, cardiac, and gastric bypass procedures. The use of a 3-D display provides a significant visualization improvement over the 2-D monitors employed in conventional laparoscopy.⁴⁴ Criticism of early stereo 3-D displays used in conventional MIS included the need for bulky shutter glasses, video helmets, and inadequate brightness.⁴⁵

While the surgeon is usually located within a few feet of the patient in the operating room, the remote-guided nature of the daVinci™ controls can allow surgery to be per-

formed from a great distance. This would allow, for example, the telemonitoring of a new procedure by local novice surgeon by experts from a remote site. This capability is facilitated by the improved visualization made possible with a stereo 3-D display.

In the current design of the daVinci™ system only the primary surgeon has the benefit of stereo 3-D viewing. Currently, a Planar StereoMirror™ monitor is being evaluated at Albany Medical Center in Albany, NY, for use as an auxiliary monitor with the daVinci system. It is being used by assisting surgeons and medical students to provide the same view of a procedure seen by the primary surgeon.

5 Summary

We have presented several examples where stereoscopic 3-D displays improve the state of medical care. In addition to increasing the diagnostic use of these displays, other medical applications include treatment planning, simulation, and patient consultation. As imaging technology continues to provide ever-more-detailed volumetric representations of the body and the steady pressure for improvement in diagnostic accuracy and treatment efficiency continues, stereopsis-based displays can provide a path to extracting information from complex medical image data with greater accuracy and in a more timely manner.

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Stereoscopic Digital Mammography: Improved Accuracy of Lesion Detection in Breast Cancer Screening

David J. Getty¹, Carl J. D'Orsi², and Ronald M. Pickett¹

¹BBN Technologies, 10 Moulton Street, Cambridge, MA 02138

²Breast Imaging Center, Winship Cancer Institute, Emory University Hospital,
Atlanta, GA 30322

Abstract. We report on a clinical trial comparing stereoscopic full-field digital mammography to standard (non-stereo) full-field digital mammography for detection of true breast lesions in a screening population. Each of 1458 enrolled patients received both a standard screening examination and a stereoscopic screening examination, which were read independently by different radiologists. Compared to standard digital mammography, stereo mammography significantly reduced false positive lesion detections by 46% ($p < 0.0001$), and significantly increased true positive lesion detections by 23% ($p < 0.05$).

Keywords: stereoscopic digital mammography, digital mammography, breast cancer screening, lesion detection.

1 Introduction

With the advent of digital mammography, high quality stereoscopic digital mammography is now a practical possibility, providing direct, in depth views of the internal structure of the breast and a potentially improved technique for breast cancer screening (1-3). Two-dimensional x-ray mammography is currently the primary screening approach for the early detection of breast cancer in women. However, it suffers from three basic limitations, which we predict stereo mammography can overcome.

The first limitation with standard mammography is that a true focal abnormality may often be undetected when masked in the 2D projections by overlying or underlying normal tissue. Masking is likely to affect the detection of focal soft tissue abnormalities that present as a mass, architectural distortion or an asymmetric density, but is perhaps even more likely to affect the detection of microcalcifications. Masking may be reduced with stereo mammography because the lesion or elements of calcium can be seen in the stereo image as separated in depth from the normal tissue aligned with it in the breast volume. This gives stereo mammography a potential advantage over standard mammography with respect to sensitivity.

The second limitation with standard mammography is the chance alignment of normal tissue, or isolated elements of calcium, at different depths within the breast, which in the 2D projected image may mimic a true focal lesion. Many of the

false-positive detections that arise in this way with standard mammography may be eliminated with stereo mammography because the superimposed tissue or calcification particles can be seen in the stereo mammogram as separated in depth. This gives stereo mammography a potential advantage over standard mammography with respect to specificity.

The third limitation is in regard to the ability to derive information about the volumetric structure of a detected lesion, information particularly important in suggesting the presence of architectural distortion and the significance of calcification clusters. For standard mammography, volumetric information can be obtained only in a limited way by cognitive merging of information taken separately from the two orthogonal 2D images. With stereo mammography, a lesion's volumetric structure is immediately and directly visualized. This difference gives stereo mammography further potential advantage over standard mammography with respect to both sensitivity and specificity.

We report here results from a clinical trial comparing standard digital mammography with stereo digital mammography for detection of true breast lesions in a screening population.

2 Methods

2.1 Subjects

Over a three year period, 1458 patients were enrolled in the clinical trial at the Emory University Breast Imaging Center in Atlanta, GA. Only female patients were eligible for enrollment, and then only if they were at elevated risk for the development of breast cancer. Our reasons for using elevated risk as a criterion for inclusion were to maximize the number of lesions and cancers detected in the study and to provide reasonable justification for the additional x-ray exposure the patients received.

2.2 Study Design

Image Acquisition. Each woman enrolled in the trial received both a standard digital mammographic screening examination and a stereoscopic digital mammographic screening examination in a single visit. The standard exam was performed using a clinical full-field digital mammography unit (GE Senographe 2000D). The stereo exam was performed on a research GE Senographe 2000D with modified x-ray collimation. Each screening exam consisted of the usual two views of each breast: cranio-caudal (CC) and medio-lateral-oblique (MLO) views. For the stereo exam, each of those two views was acquired as a stereo pair comprised of two images captured with the x-ray tube rotated by 10-degrees between the two acquisitions while the breast remained compressed and unmoved.

Image Display. The standard digital mammograms were viewed on a standard, FDA-approved, dual-monitor GE Review Workstation. The stereo mammograms were viewed on a prototype medical stereo display, the StereoMirror SD2250, developed by Planar Systems Inc (16). This stereo display, shown in Fig. 1, consists of two 5 megapixel, grayscale monitors mounted one above the other with an angular separation of 110 degrees between the two faces. The two images, each displayed on one of

the two monitors, are cross-polarized. A glass plate with a half-silvered coating is placed between the two monitor faces, bisecting the angle between them. The image presented on the lower (vertical) monitor is transmitted through the glass plate, while the image presented on the upper (angled) monitor is reflected from the top surface of the glass plate. The radiologist wears lightweight passive cross-polarized glasses such that the left eye sees only the reflected image from the upper monitor, while the right eye sees only the transmitted image from the lower monitor. The radiologist's visual system fuses the two images into a single in-depth image of the internal structure of the breast.



Fig. 1. BBN/Planar stereo display workstation

We have developed software for the stereo display that permits the radiologist to control many aspects of the displayed stereo images using a mouse and a small keypad. The radiologist can select a single stereo view for display at full resolution or, as shown in Fig. 1, both stereo views of both breasts simultaneously at half-resolution. The radiologist can control brightness and contrast, reverse black and white, enable 2X image magnification with roaming, invert depth (reversing foreground and background), and enable a stereo cursor that can be moved throughout the displayed volume.

Readers. Five board-certified radiologists, all practicing mammography fulltime, participated in the clinical trial. A Randot Stereo Acuity Test was administered to each mammographer to verify that he/she had functional depth perception and to measure his or her stereo depth discrimination acuity. The measurements showed that all five mammographers had excellent stereo depth acuity, discriminating objects in depth separated by no more than 30 seconds of arc of horizontal disparity in the stereo image.

As a control for individual differences, each of the five mammographers read approximately equal numbers of cases in the standard and stereo reading conditions. The percentage of the total number of cases read by each mammographer varied somewhat across the group, from a low of 13.8% to a high of 30.0%.

Image Interpretation. The standard and stereo digital mammograms for each patient were read independently by two different radiologists as part of the daily clinical practice. Prior mammograms were available for comparison for 99.0% of the enrolled patients. For each case, the radiologist filled out a form indicating the presence and nature of findings, if any, and the classification of the case using the BI-RADS assessment categories: 0 (recall patient for work-up), 1 (negative), 2 (benign), or, extremely rarely, 3 (probably benign). Categories 4 (biopsy suggested) and 5 (highly suggestive for malignancy) are not permitted at Emory for breast cancer screening. For each case, if both radiologists classified the case as BI-RADS 1, 2, or 3, no further action was taken. If either or both of the radiologists reported one or more findings requiring work-up (BI-RADS 0), then the two radiologists consulted to review both the standard and stereo images. If both had reported one or more findings, they sought then to determine the correspondence of findings between the two readings, and to concur on the nature of the requested work-up. However, all reported findings on stereo and/or standard mammography were worked-up whether concordant or not. All patients with reported findings requiring recall received standard (non-stereo) clinical diagnostic work-up examinations. For each worked-up finding, a final BI-RADS assessment of category 1 was truth for absence of a lesion (i.e., a false positive), while an assessment of categories 2, 3, 4, or 5 constituted truth that the finding of concern was a true lesion. Truth about the presence of cancer was determined from subsequent biopsy, if performed.

3 Results

Of the 1458 women enrolled in the trial, 282 (19.3%) were recalled for work-up of 332 findings. Standard mammography reported 216 findings while stereo mammography reported 176 findings. Of these, 60 findings were reported by both modalities. All of these patients were recalled for standard clinical (non-stereo) diagnostic work-up exams. Of the 332 reported findings, 140 (42.2%) were shown at work-up to be true focal lesions (56 BI-RADS 2; 43 BI-RADS 3; 38 BI-RADS 4; 3 BI-RADS 5) while the remaining 192 (57.8%) were shown to be false positives (BI-RADS 1).

3.1 Sensitivity of Lesion Detection

Of the 140 true lesions, standard mammography detected 86 (61.4%), missing 54 (38.6%), while stereo mammography detected 106 (75.7%), missing 34 (24.3%) (Fig. 2). Of these, 52 lesions were detected by both modalities. Thus, stereo mammography has increased true positive lesion detections by 23% and reduced false negative reports by 37 % ($p < 0.05$).

Of the 41 lesions judged at work-up to be BI-RADS 4 or 5, 35 of the lesions were biopsied. At biopsy, 18 of the lesions were found to be benign while the other 17 (48.6%) were found to be malignant. Standard and stereo mammography both detected 14 of the 17 malignancies (82.4%); 11 of the 17 (64.7%) were detected by both modalities.

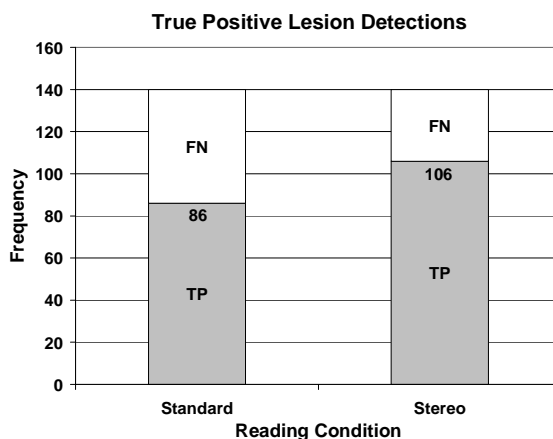


Fig. 2. Frequency of true positive (TP) detections and false negative (FN) reports for findings shown to be true lesions at work-up

3.2 Specificity of Lesion Detection

As shown in Fig. 3, of the 192 false positive detections, standard mammography was responsible for 130 (67.7%) while stereo mammography was responsible for 70 (36.5%), with 8 (4.2%) common to both. This 46% reduction in false positive reports with stereo mammography is highly statistically significant ($p < 0.0001$).

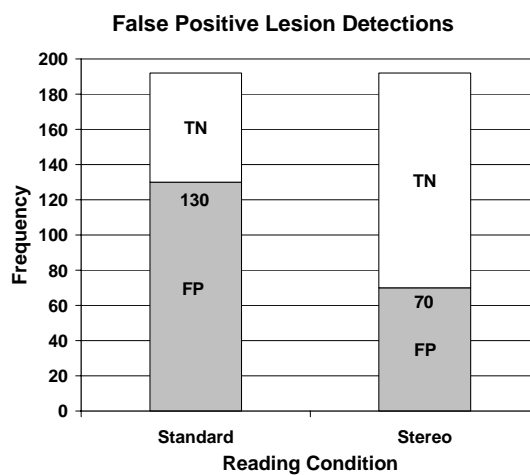


Fig. 3. Frequency of false positive (FP) reported findings and true negative (TN) reports

4 Discussion

We have analyzed the impact of stereo mammography on reading accuracy (sensitivity and specificity) and on reader confidence regarding the presence of a true lesion.

The main findings with respect to lesion detection accuracy are that stereo mammography produced a statistically significant improvement over standard mammography in both sensitivity and specificity.

With regard to specificity, stereo mammography has reduced false positive detections by almost half compared to standard mammography. We believe the large reduction in false positives is due to the fact that normal tissue or unrelated calcifications at different depths, that would be superimposed in a 2D projection and resemble a focal lesion, are seen in the stereo mammogram as layers of normal tissue or unrelated calcifications lying at different depths through the breast.

If stereo, as implemented here, were ultimately applied as a replacement for standard mammography for screening, the required doubling of the x-ray dose would be unacceptable for routine screening. However, analysis of gains in signal detectability from binocular summation in the human visual system with stereo imaging (5) suggests that the per-image dose required for a fully adequate stereo image could be reduced to nearly one half of the standard dose, and that prediction has been confirmed in a recently reported reader study using mammography phantoms (6). While this finding would have to be confirmed in a clinical setting, we expect that the effect of stereo with half-dose image pairs would be essentially the same as found here with full-dose image pairs.

The results suggest that stereo mammography could bring a substantial improvement over standard mammography in the accuracy of lesion detection and, with that, substantial gains in the cost-effectiveness of breast cancer screening. Although we did not record reading times, readers reported anecdotally that reading the stereo mammogram required less time than reading the standard mammogram.

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